The effects of non-functioning pituitary adenomas on pregnancy

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Abstract

Objective: Non-functioning pituitary adenomas (NFPAs) are a group of hormonally inactive adenomas. The aim of this study was to investigate the possible effects of NFPAs on pregnancy.

Material and Methods: Thirty patients with NFPAs and without hormone deficiency or excess were included. We retrospectively evaluated anterior pituitary hormone levels, follow-up periods, pituitary imaging findings, symptoms associated with adenoma size increase during pregnancy, adverse pregnancy outcomes, delivery procedures, pregnancy week at delivery, birth weight, and lactation duration.

Results: The mean age of the patients was 41.26±9.06 years, and the mean follow-up after diagnosis was 92.8 months. Seven were diagnosed with macroadenomas (defined as the largest diameter >10 mm) and 23 had microadenomas. There were 92 pregnancies in total. The incidence of nausea-vomiting and visual impairment during pregnancy were more common in the macroadenoma group (p=0.016 and p=0.042, respectively). Spontaneous pregnancy rates were high. The patients with NFPAs did not have an increased risk of pregnancy-related complications compared to the general population, and there were no obvious negative effects on fetal development or lactation. NFPAs were not associated with an increased cesarean section rate.

Conclusion: These findings suggest that NFPAs, even macroadenomatous NFPAs, have no negative effects on pregnancy outcomes, fetal development, or lactation. (J Turk Ger Gynecol Assoc. 2025; 26: 20-5)

Keywords: Pituitary, pregnancy, non-functioning pituitary adenomas, adenoma

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Introduction

Pituitary adenomas that are not hormonally active are referred to as clinically non-functioning pituitary adenomas (NFPAs). Pituitary adenomas are relatively common, with 80-100 cases per 100,000 population, with NFPAs making up 15-30% (1). Currently, NFPA is detected either because of the mass effect of a macroadenoma or, increasingly, incidentally during an imaging procedure, a condition known as pituitary incidentaloma (2). Pregnancy alters the structure and function of the pituitary gland. Due to lactotroph hyperplasia, during pregnancy the anterior and total pituitary volume significantly increase and remain larger in the first post-partum year (3). This growth may cause a risk of visual impairment, particularly with macroadenomas or adenomas close to the optic chiasm. In the event of the emergence of symptoms such as headache, visual impairment, ophthalmoplegia, nausea and vomiting, and altered consciousness, pituitary apoplexy, which is a rare but potentially life-threatening condition, should be considered as a potential diagnosis (4).

Research evaluating the relationship between NFPAs and pregnancy is fairly limited (4-6). The current guidelines recommend evaluating the size of the adenoma and its proximity to the optic pathways when considering surgery during the preconceptional period. This approach helps reduce the likelihood of adenoma growth and the risk of

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infertility. It has been stated that individuals with non-functional microadenomas do not require routine monitoring throughout pregnancy due to their low growth potential (7).

In this study, we aimed to investigate the impact of NFPAs on pregnancy and related conditions, focusing on aspects such as symptoms due to adenoma size during pregnancy, delivery procedures, adverse pregnancy outcomes, and lactation duration.

Material and Methods

The study was a retrospective cross-sectional design. The study population included patients with a diagnosis of benign neoplasm of the pituitary gland who presented to our institution between January 2009 and November 2022. Of 12,277 patient records initially screened (excluding male patients and duplicates), there were 1,906 female patients. Incomplete records, functional pituitary adenomas, and patients with hormonal deficiencies were excluded, based on clinical and laboratory findings. This resulted in an eligible study cohort of 119 patients with NFPA who met the inclusion criteria. The patient's understanding and confidentiality were discussed by calling the patients by phone and explaining the purpose, content and method of the study to the patient by the same physician throughout the interview. Of the 86 patients who were successfully contacted, those meeting any of the following exclusion criteria were removed from the study: male infertility in their spouse, polycystic ovary syndrome, infertility due to a tuboperitoneal anomaly, or uterine anomalies (either congenital or acquired). After applying these criteria, the remaining patients were fully informed about the study's objectives and methodology. Ultimately, 30 patients with NFPA who met the inclusion criteria and provided verbal informed consent were included in the final analysis.

The study collected various data from patients, including gestational age, presence of other diseases, regular medication use, duration of follow-up for NFPA before pregnancy, and the cycle in which pregnancy occurred after contraception. Patients were also asked about the method of conception (spontaneous or assisted reproduction). In addition to these data, patients were specifically questioned about symptoms experienced during pregnancy, particularly those suggestive of pituitary apoplexy. These included nausea and vomiting during the second and third trimesters, headache, ophthalmoplegia, visual impairment, and altered consciousness. Detailed information was gathered to determine the onset, severity, and progression of these symptoms, helping to better understand their relationship to adenoma size and potential growth during pregnancy. Furthermore, obstetric history was obtained, including gravida, parity, abortion, miscarriage, and live or stillbirth outcomes. Data on additional obstetric complications, such as gestational diabetes mellitus (GDM), pregnancy-related hypertension, and preeclampsia, were also collected. Delivery details (miscarriage, live birth, or stillbirth), gestational age at delivery, mode of delivery, newborn health, birth weight, and lactation duration were recorded for comprehensive analysis.

Statistical analysis

Data analysis was performed using the SPSS for Windows 15 software package (IBM Corporation, Armonk, NY, USA). The normal distribution of variables was assessed using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive statistics are presented as median and range for non-normally distributed variables, mean ± standard deviation for normally distributed variables, and number of cases and percentages for nominal variables. Fisher's exact test was used to compare categorical variables, while the Mann-Whitney U test was used to compare independent variables that were non-normally distributed between the two groups. Patients with macroadenoma, defined as an adenoma with the largest diameter of >10 mm, and microadenoma were compared using crosstabs for abortion, stillbirth, ectopic pregnancy, nausea, vomiting, headache, and visual impairment. Pearson's chi-square or Fisher's exact test was used depending on whether there was a difference between the groups regarding these frequencies and when the values observed in the cells did not meet the chi-square test assumptions. A significance level of $p<0.05$ was used to determine statistical significance.

Results

Of the 30 patients with NFPA, 7 (23.3%) had macroadenomas, and the longest median (range) diameter of these adenomas was 12 (11-18) mm, while 23 had microadenomas. Patients' current mean age was 41.3±9.1 years and NFPA follow-up duration was a mean of 92.8±56 months. In total there were 92 pregnancies recorded. Twelve (%) had undergone an elective abortion, three (%) cases were ectopic pregnancies (mean 7.3 weeks), seven (%) were missed abortions (mean 9.1 weeks), four (%) were stillbirths (mean 25 weeks), and 66 (%) resulted in live births.

Table 1 shows the characteristics of gestational age, birth weight, week of birth, lactation duration, adenoma-related symptoms, pregnancy complications, delivery method, and outcomes of live births. There were preterm births (before 37 completed weeks) in 21.2% of live births. Of all the live births, 9% were macrosomic, and 12% had low birth weight. Regarding lactation, the median duration was 18 (0-30) months, with 12% of patients having a lactation period of six months or less without an identifiable cause, and two pregnancies had no lactation.

Thirteen of the 92 pregnancies occurred in patients with NFPA before pregnancy. Among these patients, one experienced a missed abortion at 6 weeks, and the remaining 12 pregnancies resulted in live births. The characteristics and outcomes of these live births are presented in Table 2. The median duration from contraception withdrawal until conception was 2.5 (1-12) months, and no patient used assisted reproductive techniques. Preterm births occurred in two pregnancies, accounting for 16.6% of all live births, while low birth weight was observed in two infants (16.6%). None of the infants exhibited macrosomia.

Table 3 compares the rates of missed abortion, ectopic pregnancy, and stillbirth in the macroadenoma and microadenoma groups for all pregnancies except elective abortions. The incidence of missed abortion was 6.3% in the macroadenoma group and 9.4% in the microadenoma group (p=0.573). Ectopic pregnancy occurred in 0% of the macroadenoma group and 4.7% of the microadenoma group, but again this was not significant (p=0.507). Similarly, stillbirth occurred in 0% of the macroadenoma group and 4.7% of the microadenoma group, and the difference was not significant (p=0.507).

Table 4 compares the frequencies of symptoms in pregnancies resulting in live births between the macroadenoma and microadenoma groups. Nausea and vomiting were significantly more frequent in the macroadenoma group (28.6%) than in the microadenoma group (3.8%) (p=0.016). Vision impairment was significantly more common in the macroadenoma group (14.3%) than in the microadenoma group (0%, p=0.042). Headache was reported in 28.6% of the macroadenoma group and 17.3% of the microadenoma group, but the difference was not significant (p=0.450). The study also screened for signs of ophthalmoplegia, changes in consciousness, and apoplexy, and none were observed in any of the pregnancies.

The comparison of pregnancies resulting in a live birth for the week of birth, birth weight, and lactation period are shown in Table 5. The median birth weight was 3200 (2500-4500) grams in the macroadenoma group and 3500 (1200-4900) grams in the microadenoma group (p=0.551). The median birth week was 38.5 (35-40) weeks in the macroadenoma group and 39 (29-41) weeks in the microadenoma group (p=0.955). The median lactation period was 18 (0-30) weeks in the macroadenoma group, and 18 (2-24) weeks in the microadenoma group (p=0.786). Overall, none of the differences between the two

Table 1. Outcomes and characteristics of live births (n=66)

	Median	Minimum-maximum
Age of gestation (year)	23.5	16-38
Birth weight (grams)	3470	1200-4900
Week of birth (week)	39	29-41
Lactation duration (month)	18	0-30
	n	**%**
Nausea-vomiting	6	9.1
Headache	13	19.7
Vision impairment	2	3
Ophthalmoplegia	0	0
Altered consciousness	0	0
Apoplexy	0	0
Pregnancy-related complications		
Pregnancy-related hypertension	4	6.1
Preeclampsia	1	1.5
Gestational-diabetes mellitus	4	6.1
Birth method		
Spontaneous vaginal delivery	40	60.6
Cesarean section	26	39.4
In vitro fertilization	2	3
Insemination	1	1.5
Spontaneous pregnancy	63	95.45

Table 2. Characteristics and outcomes of live births of patients with known pre-pregnancy non-functional pituitary adenoma diagnosis (n=12)

	Median	Minimum-maximum
Age of gestation (years)	30	21-35
Pre-pregnancy follow-up period (months)	48	12-120
Total follow-up period (months)	120	36-252
Birth weight (grams)	3225	2300-3840
Week of birth (weeks)	38	35-40
Lactation duration (months)	14	2-24
	n	**%**
Nausea-vomiting	3	25
Headache	3	25
Vision impairment	1	8.3
Ophthalmoplegia	0	0
Altered consciousness	0	0
Apoplexy	0	0
Pregnancy-related complications		
Pregnancy-related hypertension	0	0
Preeclampsia	0	0
Gestational-diabetes mellitus	0	0
Birth method		
Spontaneous vaginal delivery	7	58.3
Cesarean section	5	41.6
In vitro fertilization	0	0
Insemination	0	0
Spontaneous pregnancy	12	100

Table 3. Comparison of outcomes of pregnancies except for elective abortion*

	Macroadenoma, (n=16)	Microadenoma, (n=64)	Total, (n=80)	p
	n (%)	n (%)	n (%)	
Missed abortion	1 (6.3)	6 (9.4)	7 (8.8)	0.573
Ectopic pregnancy	0 (0)	3 (4.7)	3 (3.8)	0.507
Stillbirth	0 (0)	3 (4.7)	3 (3.8)	0.507
*Column percentages are given. ** Fisher's exact test was used				

Table 4. Comparison of symptoms seen in pregnancies resulting in live birth*

	Macroadenoma, (n=14)	Microadenoma, (n=52)	Total, (n=66)	p
	n (%)	n (%)	n (%)	
Nausea-vomiting	4 (28.6)	2 (3.8)	6 (9.1)	**0.016****
Headache	4 (28.6)	9 (17.3)	11 (6.7)	0.450**
Vision impairment	2 (14.3)	0 (0)	2 (3.0)	**0.042****
*Column percentages are given. **Fisher's exact test was used				

Table 5. Comparison of pregnancy outcomes and lactation in patients with macroadenoma and microadenoma

	Macroadenoma, (n=14)	Microadenoma, (n=52)	p*
	Median (minimum-maximum)	Median (minimum-maximum)	
Week of birth (week)	38.5 (35-40)	39 (29-41)	0.955
Birth weight (gram)	3200 (2500-4650)	3500 (1200-4900)	0.551
Lactation duration (month)	18 (0-30)	18 (2-24)	0.786
*Mann-Whitney U test was used for comparison			

groups were significant for birth weight, birth week, or lactation period.

Discussion

There is limited data available on the relationship between NFPAs and pregnancy. To address this gap, we conducted a study to investigate the effects of NFPAs on pregnancy and related factors. We focused on examining symptoms caused by adenoma size during pregnancy, delivery procedures, adverse pregnancy outcomes, and lactation duration.

According to the Türkiye Demographic and Health Survey 2018 (TNSA-2018), from 2013 to 2018, 6% of pregnancies resulted in elective abortion, 13% in a missed abortion, 1% in a stillbirth, and 80% in a live birth (8). To assess the potential complications and mortality rates associated with childbirth, it is essential to consider the national data specific to the country, and we analyzed our data in this manner. Our findings suggest that NFPA does not significantly affect the rates of elective and missed abortions, as they were similar to the national averages. The incidence of stillbirths in the study population (4.3%) was higher than the national average (1%), but this was not significant and the cohort size was small. Confirmation of these data is needed, and if verified, additional research is required to investigate the underlying mechanisms. Twelve percent of all live births in our study were of low birth weight, a figure that mirrors the national rate of 12%; similarly, the average lactation duration in our sample was 16 months, closely aligning with the median breastfeeding duration of 16.7 months reported in national data. Nevertheless, caution must be exercised when interpreting these relationships, as the small sample size and the absence of detailed sociodemographic data may limit the generalizability of these findings. Thus, the results should be viewed as suggestive rather than definitive. This study highlights the need for further research, particularly into the potential impact of pituitary adenomas on pregnancy outcomes, as the current data, while informative, are not robust enough to fully elucidate the complexity of these associations.

Obstetric problems in the general population, such as GDM, occur at a rate of 0.06-15% (9), pregnancy-related hypertension occurs at a rate of 6-10% (10), and preeclampsia occurs at a rate of 3-5% (11). The rates in our cohort were similar to these figures in the general population. Regarding the chosen delivery method, 26 (39.4%) patients were delivered via cesarean section. Our national rate of elective Cesarean sections is higher at 47.5% (12). UK researchers found that 50% of individuals with NFPA underwent cesarean delivery, compared to 24% of the general population (4). However, our study did not find

any evidence of an increased risk of cesarean section in these patients, despite high rates nationally. The mean birth weight in our study was 3154 grams with a similar median value of 3225 grams, ranging from 2300-3840. It was 2500 g or less in only two cases (16.6%). Karaca et al. (5) reported that one in six live births (16.6%) were macrosomic, but no additional problems were detected. No adverse effects of NFPA on fetal development have been demonstrated.

An increase in the size of NFPAs has been reported on rare occasions due to tumor growth, infarction, or hemorrhage during pregnancy (4,6,13). Karaca et al. (5) performed an MRI of the pituitary in one patient, and the adenoma did not enlarge. No compression symptoms were observed during pregnancy. Comparing pregnancy characteristics between patients with macroadenoma and microadenoma, our data show no significant differences between the two groups regarding the frequency of missed abortions, ectopic pregnancies, and stillbirths. However, headaches were seen in 17.3% of the microadenoma group and 28.6% of the macroadenoma group. Although this difference was not statistically significant, the higher incidence in the macroadenoma group may be associated with adenoma enlargement caused by lactotroph cell hyperplasia during pregnancy and/or an increase in dural pressure caused by the macroadenoma, as reported in the literature (14). The significantly higher incidence of visual disturbances in the macroadenoma group may be due to optic chiasm compression. However, we did not observe apoplexy, altered consciousness, or ophthalmoplegia, which are rare complications reported in the literature. There were no statistically significant differences among live births in gestational age, birth weight, and duration of lactation between the groups. Our findings did not demonstrate a correlation between adenoma size larger than 10 mm, that is macroadenoma by definition, and unfavorable pregnancy outcomes.

There were 13 (14%) of 92 pregnancies occurred in patients who had a pre-existing NFPA before pregnancy. One of the pregnancies resulted in a missed abortion in the sixth week. No ectopic pregnancy or stillbirth was observed, and the remaining 12 pregnancies resulted in live births. The patient with the missed abortion had a microadenoma. Of the pregnancies that resulted in live births, three had macroadenomas, and nine had microadenomas. No symptomatic growth or mass effect was observed in any patients during pregnancy in our study. Although a size increase in NFPA is rare during pregnancy, visual loss and apoplexy have been reported (15,16). However, according to the literature and our study, the risk of symptomatic growth appears to be very low, especially in microadenomas (4,5,17).

The literature suggests that an NFPA can impact fertility and result in rare pregnancies due to the effects of gonadotropin production and hyperprolactinemia (18). In the study by Karaca et al. (5), spontaneous pregnancy occurred in seven patients (87.5%), one of whom was using cabergoline and six patients were receiving no treatment. In contrast, one secondary hypogonadism patient became pregnant with ovulation induction. Our high spontaneous pregnancy rates may be because patients with hypogonadotropic or hypergonadotropic hypogonadism and hyperprolactinemia were excluded, and only those with a normal hormone panel were included. Furthermore, there was a lack of data for women with NFPA who did not have to conceive. Consequently, our data is insufficient to conduct a thorough examination of the correlation between NFPA and fertility.

Study limitations

The most significant limitations of our study include the small sample size and the difficulty in accessing all data due to the retrospective design. Although the lack of a control group is a limitation, we compared our findings with national data. Furthermore, we excluded patients with hormonal abnormalities and a history of medical treatment to minimize confounding factors. This resulted in a selected population for evaluating the effects of NFPAs on pregnancy. Of the 66 pregnancies resulting in live births in our study, 13 were in women with a pre-existing diagnosis of NFPA, while the remaining 53 pregnancies occurred before the diagnosis. However, since all of these patients were asymptomatic, there may have been a delay in the diagnosis, and adenomas may have been present during the pregnancies.

Conclusion

This study indicated that symptoms suggestive of adenoma growth during pregnancy are more prevalent in patients with macroadenoma than in those with microadenoma. However, further research is necessary to establish whether these symptoms are an effect of the tumor growth. Our findings suggest that NFPAs did not have any adverse effects on pregnancy outcomes, fetal development, or lactation.

Ethics

Ethics Committee Approval: *The study received approval from the Ethical Committee of Ankara University Faculty of Medicine (approval number: İ5-227-19, date: 14.11.2019).*

Informed Consent: *Informed consent were obtained.*

Footnotes

Author Contributions: *Surgical and Medical Practices: Ö.B.A., Ö.D., A.G.C., D.Ç., Concept: Ö.B.A., Ö.D., A.G.C., D.Ç., Design: Ö.B.A., Ö.D., A.G.C., D.Ç., Data Collection or Processing:*

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