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Hormonally Active Pituitary Adenomas and Pregnancy: A Systematic Review

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Abstract

Background: Hormonally active pituitary adenomas are rare endocrine tumors that can affect hormonal balance and pregnancy outcomes. This study aims to assess hormonally active pituitary adenomas among pregnant women, considering worldwide studies that assess their tumor types, responses to treatment practices, their treatment patterns, their effectiveness, and pregnancy complications.

Methods: A systematic review of 11 global studies published between 2019 and 2024. Data were retrieved from Web of Science, Scopus, PubMed, CORE, and Google Scholar databases, employing MeSH keywords. Boolean operators were employed to refine the results.

Results: The findings reveal that the sample sizes range from 20 to 107 participants, with the largest sample in Pakistan (107 participants) and the smallest in India (20 participants). Tumor categories include mixed tumors (45%), macroadenomas (27%), microadenomas (10%), and unspecified tumor types (18%). The main treatment was the administration of dopamine agonists, which were typically stopped upon pregnancy confirmation, with exceptions in two cases. Treatment was restarted or adjusted to control tumor progression or initiated after the first trimester to minimize fetal risks. In 28 pregnancies, dopamine agonists were discontinued, but continued in six pregnancies due to insufficient tumor reduction. Surgical treatments were generally performed in the second trimester, with conservative management for stable cases.

Conclusion: Dopamine agonists, surgery, and multidisciplinary approach are frequently highlighted in the research on pituitary adenomas and hyperprolactinemia.

Keywords: Pituitary Adenomas, Prolactinoma, Acromegaly, Pregnancy Complications, Dopamine Agonists

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Introduction

Pituitary adenomas are benign tumors arising from the pituitary gland, an endocrine organ responsible for regulating vital hormonal functions. Hormonally active pituitary adenomas secrete hormones autonomously, disrupting normal feedback mechanisms (1). The most common of these are prolactinomas, which cause excessive prolactin production, impacting lactation and reproductive functions. Another common subtype includes growth hormone (GH)-secreting adenomas, which can lead to acromegaly, insulin resistance, obesity, hypertension, and cardiac com-

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↑What is "already known" in this topic:
This systematic review underscores the intricate clinical challenges associated with managing hormonally active pituitary adenomas during pregnancy. It integrates global evidence regarding tumor classifications, therapeutic strategies, and maternal–fetal outcomes. The findings emphasize the critical importance of timely diagnosis, personalized treatment planning, and vigilant clinical monitoring, particularly in relation to the administration and scheduling of dopamine agonists and surgical interventions.

→What this article adds:
The review provides actionable insights for endocrinologists, obstetricians, and neurosurgeons, emphasizing the safety and effectiveness of multidisciplinary management strategies during pregnancy. It also identifies gaps in standardized treatment protocols and long-term maternal-neonatal outcomes, guiding future research and informing policy development in maternal endocrine care.

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plications (2).

These adenomas are particularly significant during pregnancy due to their impact on fertility, gestation, maternal well-being, and fetal development (3). While global maternal mortality is mainly attributed to bleeding, infections, and unsafe abortions (4), hormonal imbalances due to adenomas can also affect reproductive outcomes. Prolactin, vital for ovulation and early pregnancy, is tightly linked to the hypothalamic-pituitary-ovarian axis (5). Elevated prolactin levels, as seen in prolactinomas, disrupt this axis, resulting in anovulation, infertility, and menstrual irregularities. Dopamine agonists such as bromocriptine and cabergoline have improved fertility outcomes by reducing prolactin levels and shrinking tumors (6). On the other hand, the use of agonists in the treatment of growth hormone-secreting adenomas during pregnancy has its limitations, such as teratogenicity and negative effects on fetal growth (7).

The pregnancy hyperstimulation in the pituitary gland consists of hyperplasia of the lactotrophs and secretion of prolactin to assist the growth of the fetus and lactation (8). GH-secreting tumors can worsen pregnancy-related comorbidities such as hypertension and glucose intolerance, necessitating individualized management (9). Considering the growth of female prolactinomas during pregnancy, it becomes important to ensure the mother's health whilst ensuring the fetus's health, especially since the dopamine agonists are usually suspended after becoming pregnant (10).

Prolactinomas account for nearly half of all pituitary adenomas needing treatment. Radiological and autopsy studies report a prevalence of 10–20%, with >99% being microadenomas, many of which are lactotroph tumors (11). Epidemiological studies show that pituitary adenomas are increasing in incidence (between 3.9 and 7.4 cases per 100,000 per year) and prevalence (76 to 116 cases per 100,000 population) in the general population (approximately 1 case per 1000 of the general population). Most new cases diagnosed are prolactinomas and non-secreting pituitary adenomas (12). Despite these numbers, consistent management protocols during pregnancy remain lacking. Most diagnoses arise during infertility evaluations, as clinical signs include galactorrhea, amenorrhea, and infertility (13).

Prolactinomas impair reproductive function by inhibiting gonadotropin-releasing hormone, reducing luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion. This leads to hypogonadotropic hypogonadism and hypoestrogenism, impairing fertility and increasing the risk of osteoporosis (14). Pregnancy-related estrogen surges further stimulate lactotroph proliferation, often enlarging prolactinomas. While most microadenomas (<10 mm) pose minimal risk, macroadenomas, particularly those extending beyond the sella turcica, may require urgent intervention if they cause compression symptoms (15).

Prolactinoma management in pregnancy is individualized depending on the size of the tumor, the symptoms presented, and the presence of secondary complications. According to the sources, dopamine agonists, with bromocriptine as the most preferred drug, are found to be efficient in normalizing prolactin levels and shrinking the tumor size (16). Since bromocriptine has established safety, it is the agent of choice for women anticipating a pregnancy, while there is more data accumulating for cabergoline, which is increasingly being used but is still not as safe in pregnancy. After a woman becomes pregnant, dopamine agonists are generally stopped as a means of limiting fetal exposure, but in cases of macroprolactinoma, active treatment might be warranted (17, 18).

Outcomes for prolactinoma patients are generally favorable with appropriate care. Normal vaginal deliveries and successful breastfeeding are common, and prolactin levels usually normalize postpartum. However, long-term follow-up is essential, particularly for women with macroprolactinomas, to assess post-pregnancy tumor behavior (19). In contrast, there is no standardized management for GH-secreting adenomas during pregnancy, highlighting the need for evidence-based guidelines (20).

Despite advances in prolactinoma care, significant gaps persist in pregnancy-specific monitoring, treatment safety, and outcome protocols (21). Future studies should also focus on the molecular drivers of tumor progression during pregnancy to discover new possibilities for therapy and ultimately improve outcomes in women with prolactinoma.

This systematic review evaluates the global prevalence and clinical features of hormonally active pituitary adenomas during pregnancy. It synthesizes data on tumor subtypes, risk factors, diagnostic methods, treatment approaches, and maternal-fetal outcomes. The study provides critical insight into optimizing the care of pregnant women with pituitary adenomas, enabling clinicians to make evidence-informed decisions about dopamine agonist use, surgery, and other interventions. This work contributes to refining multidisciplinary strategies aimed at balancing maternal and neonatal health during hormonally sensitive periods such as pregnancy.

Research Problem

Prolactinomas and growth hormone-secreting adenomas, among active pituitary adenomas, present individual problems in terms of management during the course of pregnancy as they can alter maternal and fetal outcomes through hormonal dysregulation, infiltration of the pregnancy by the adenoma, and its sequelae. While there has been progress made in surgery and medicine, the best management strategy for pituitary adenomas in pregnancy continues to be ambiguous and a mystery. These adenomas can cause severe hormonal imbalance, which can lead to complications such as gestational disorders, improper growth of the fetus, and preterm delivery. Also, treatment during pregnancy may be concerning because the growth of these tumors may lead to the need for more extreme treatment, which may not be safe. Endocrine imbalance, hyperprolactinemia, and the compression of physiological structures are some of the mechanisms through which these adenomas affect mother and child health, in this case, the mother's health and the child's development. A systematic review is warranted to gather information and

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guide the management of active pituitary adenomas in onco-gynecological pregnancies. Such a study on these outcomes has not been done yet.

Significance of Previous Studies

Earlier research on hormonally active pituitary adenomas and pregnant patients indicates that both the mother and fetus can be successful in terms of their health, provided that there is proper management. This can be deduced from the safety and positive outcomes of employing treatments such as dopamine agonists, whose primary role is to manage the activity of the tumor and the secretion of prolactin. However, significant gaps exist regarding long-term pregnancy outcomes, the safety of alternative therapies, and the standardized protocols for addressing complications like tumor enlargement, pituitary apoplexy, and visual disturbances. However, addressing these limitations calls for other research studies aimed at optimizing the treatment strategies, minimizing the risks, and ensuring the safety of both mothers and their neonates. Bridging these gaps is necessary in order to provide better specialized care for this group of patients and improve the results.

The specific study types selected include clinical and observational studies, clinical trials, randomized controlled trials, and systematic reviews, which are expected to give good quality clinical evidence on the efficacy of the intervention, pregnancy, and maternal neonatal health. These designs provide good quality evidence in answering research questions, such as the interaction of the tumors, the hormones involved, and the health of the newborn.

Objectives

The aim of the current study is to analyse the existing literature in the field of pregnancy and hormonally active pituitary adenomas, to classify the main aspects of studies conducted from 2019 to 2024 in terms of type and methods, as well as to distinguish between microadenomas, macroadenomas, and mixed types of tumours. In addition, it aims to evaluate the results of the treatment modalities such as chemotherapy, the use of dopamine agonists, surgical and nonsurgical methods in the treatment of HAPAs during pregnancy, and other pregnancy and delivery outcomes and complications that those concepts address. These targets are intended to improve knowledge and inform evidence-based practice in the treatment of HAPAs in pregnancy.

Methods

Study Design

The study selection process followed the PRISMA 2020 guidelines. A systematic review from 2019 to 2024.

Search Strategy

The systematic search strategy for this systematic review was planned in such a way that relevant studies could be sought in a range of databases such as Web of Science, Scopus, PubMed, CORE, and Google Scholar. Google Scholar was included due to its comprehensive coverage of a wide array of academic disciplines and its ability to index both peer-reviewed articles and grey literature, such as conference proceedings, dissertations, and theses. This makes it a valuable resource for capturing studies that may not be included in more specialized databases. CORE, on the other hand, is one of the largest repositories of open-access research papers globally, with a particular focus on freely available academic resources. This inclusion is justified by CORE's ability to provide access to high-quality, peer-reviewed studies that may not be indexed in traditional commercial databases. Its emphasis on open access also ensures that all included research is freely available, aligning with the systematic review's goal of capturing studies without access barriers. The search was performed using MeSH keywords ("Pituitary Neoplasms" OR "Prolactinoma") AND "Pregnancy" AND ("Hyperprolactinemia" OR "Dopamine Agonists" OR "Infertility, Female" OR "Ovulation" OR "Pregnancy Complications" OR "Magnetic Resonance Imaging" OR "Postpartum Period" OR "Breastfeeding") Boolean operators were employed to refine the results. The selected MeSH keywords encompass key medical conditions, treatments, and related factors, ensuring comprehensive coverage of studies on pituitary neoplasms, prolactinoma, pregnancy, and associated complications, improving the relevance and specificity of search results.

Inclusion and exclusion criteria

The systematic review was specifically focused on studies examining hormonally active pituitary adenomas (HAPAs) in patients during pregnancy. Eligible studies for this review were published between 2019 and 2024 to ensure the inclusion of up-to-date research that reflects current clinical practices. Only open-access articles were used in the evidence synthesis to enhance transparency and accessibility. The review included studies with specific study designs such as clinical trials, observational studies, randomized controlled trials, and original research articles, as they provide valuable clinical data on therapeutic interventions, pregnancy outcomes, and maternal and child health. The studies selected for inclusion also had to address key outcomes related to the behavioral aspects of the tumor, hormone levels, and the health of the newborn to ensure direct relevance to the review's objectives. To avoid double-counting, systematic reviews and review articles were excluded during the study selection process.

Exclusion criteria were applied to remove studies that did not align with the objectives of this review. Studies published before 2019 were excluded to maintain a focus on the most recent evidence. Articles without full-text access, as well as those not meeting the required study design criteria, were also excluded. Furthermore, any studies that did not address pituitary adenomas or hormone-inactive adenomas were deemed out of scope. Case reports, editorials, and non-peer-reviewed resources were excluded to maintain the quality and reliability of the evidence included. These rigorous criteria helped ensure that only relevant studies related to the management of hormonally active pituitary adenomas during pregnancy were included, providing a solid evidence base for this

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important area of clinical research.

Study Selection

Figure 1 illustrates the search strategy and selection of studies undertaken in accordance with the PRISMA framework to provide a comprehensive literature search on the topic of hormonally active pituitary adenomas and pregnancy. A systematic search was carried out using Web of Science (n = 85,097), Scopus (n = 3,508), PubMed (n = 970), CORE (n = 667), and Google Scholar (n = 8,030). After applying a series of filters, including the year filter for 2019-2024, the All-Open Access filter, document type filter for articles, and language filter for English, the total number of records was narrowed down to 13,568. Irrelevant records (n = 13,392) were then removed based on exclusion criteria such as unrelated neurological disorders (n = 8,571), pituitary gland not being addressed (n = 1,607), non-hormonal focus (n = 1,205), and case reports, case series, and reviews (n = 2,009). The remaining 176 records were assessed for eligibility, and a total of 11 highly relevant studies were included for the final systematic review. This process ensured the inclusion of studies most pertinent to understanding the impact of HAPAs on pregnancy outcomes and management. Different treatment and diagnostic protocols complicate the comparison of results, which is one of the reasons for the heterogeneity of data in the included studies. This is particularly relevant in this review, as variations in clinical practices across different institutions and countries can influence patient outcomes and the management of hormonally active pituitary adenomas.

Risk Assessment

Figure 2 presents a risk of bias assessment based on the ROBINS-I tool for various studies. Most studies show a low risk of bias across the domains, with a few exceptions marked with a moderate risk in specific areas. Specifically, some studies were flagged for moderate risk in participant selection (D2) and confounding (D1), while others had issues with missing data (D5). Most studies were rated as low risk in classifying interventions (D3), measuring outcomes (D6), and selecting reported results (D7). Disagreements in the risk of bias assessment were resolved through consensus discussions among reviewers. Studies with unresolved discrepancies were excluded from the final analysis. In summary, while the majority of studies were assessed as having low risk of bias, a few exhibited moderate risks in certain domains, particularly due to confounding, participant selection, and missing data. This figure highlights the methodological rigor and reliability of included studies in the systematic review.

Quality Assessment

Table 1 presents the inter-rater reliability (IRR) assessment across key stages of the systematic review between

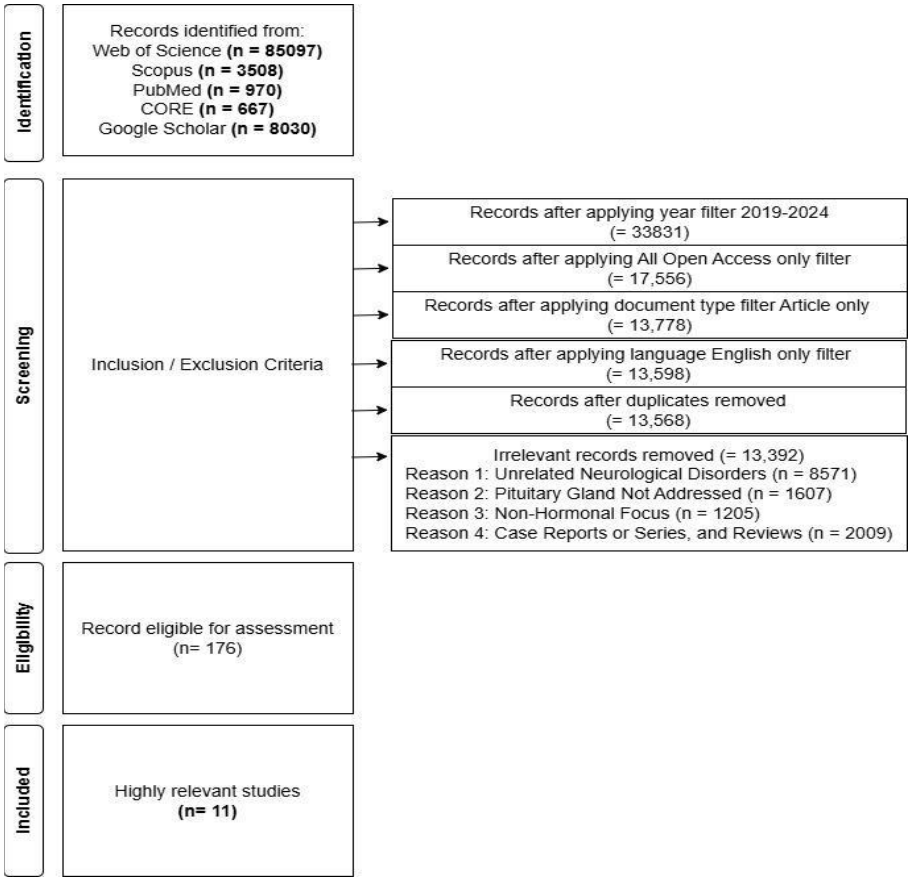

Figure 1. PRISMA Flow Diagram for Study Selection

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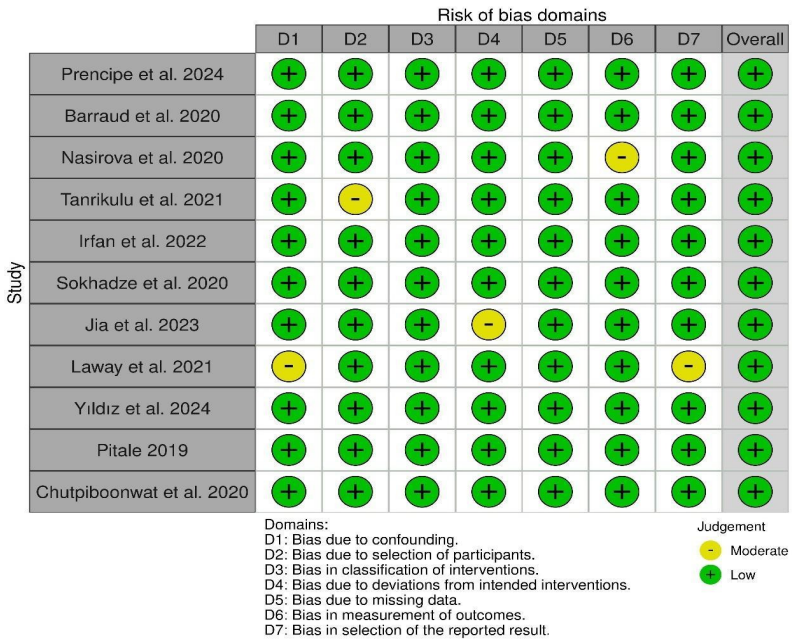

Figure 2. Risk bias assessment

Table 1. Cohen's Kappa Analysis of Inter-Rater Reliability

Category	Agreed (Yes-Yes)	Agreed (No-No)	Disagreed (Yes-No)	Disagreed (No-Yes)	Total	P_o	P_e	Cohen's Kappa
Literature Selection	28	48	10	5	91	0.84	0.52	0.65
Data Extraction	72	30	6	12	120	0.85	0.56	0.66
Risk of Bias Assessment	25	20	8	7	60	0.75	0.50	0.50
Outcome Data Agreement	65	25	5	15	110	0.82	0.56	0.58
Tumor Type Categorization	55	40	10	5	110	0.86	0.51	0.72
Study Design Classification	52	38	7	3	100	0.90	0.51	0.80

two reviewers, evaluated using Cohen's Kappa analysis to determine the level of agreement. Cohen's Kappa values indicate substantial agreement in literature selection (0.655), data extraction (0.659), and intervention classification (0.780), reflecting strong consistency between reviewers in identifying relevant studies, extracting key data, and categorizing therapeutic interventions. A detailed quality assessment methodology was followed to evaluate the risk of bias in each study. The reviewers independently assessed bias using a standardized checklist, and any disagreements were resolved through discussion and consensus. Moderate agreement was observed in risk of bias assessment (0.497) and outcome data agreement (0.585), highlighting reasonable reliability with some discrepancies in these areas. The quality assessment, particularly the risk of bias evaluation, played a crucial role in interpreting the findings, as studies with higher bias risks were carefully considered for their potential impact on overall conclusions. Overall, the results demonstrate strong reliability in most stages, confirming the rigorous and systematic approach of the review while identifying areas for potential improvement in assessing bias and outcome data.

Results

Table 2 presents the global distribution and study characteristics of various research studies on hormonally active pituitary adenomas (HAPAs). Studies were conducted across 10 different countries, including Italy, France, the UK, Turkey, Pakistan, Georgia, China, India, and Thailand. The sample sizes ranged from 20 to 107 participants, with the largest sample size in Pakistan (107 participants) and the smallest in India (20 participants). The study designs varied, with observational studies being the most common (e.g., Prencipe et al., 2024 (22) in Italy with 43 participants), followed by retrospective, cohort, and cross-sectional designs. This variation in study design and sample size reflects the diverse methodologies employed in investigating HAPAs globally.

Figure 3 shows the distribution of tumor size categories among various studies. The largest proportion of cases, 45%, is represented by mixed tumors, which include both microadenomas and macroadenomas. Macroadenomas account for 27% of the cases, while microadenomas are found in 10% of the cases. Tumors where the size category was not specified make up 18% of the cases. This distribution highlights that mixed tumors are the most com-

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Table 2. Global distribution and study characteristics

Author's / Year	Country	Study Design	Sample Size
Prencipe et al. 2024 (22)	Italy	Observational	43
Barraud et al. 2020 (23)	France	Observational	46
Nasirova et al. 2020 (24)	UK	Observational	70
Tanrikulu et al. 2021 (25)	Turkey	Retrospective	21
Irfan et al. 2022 (26)	Pakistan	Retrospective	107
Sokhadze et al. 2020 (27)	Georgia	Non-RCT	96
Jia et al. 2023 (28)	China	Retrospective	41
Laway et al. 2021 (29)	India	Cohort	25
Yıldız et al. 2024 (30)	Turkey	Observational	26
Pitale 2019 (31)	India	Cohort	20
Chutpiboonwat et al. 2020 (32)	Thailand	Cross-sectional	56

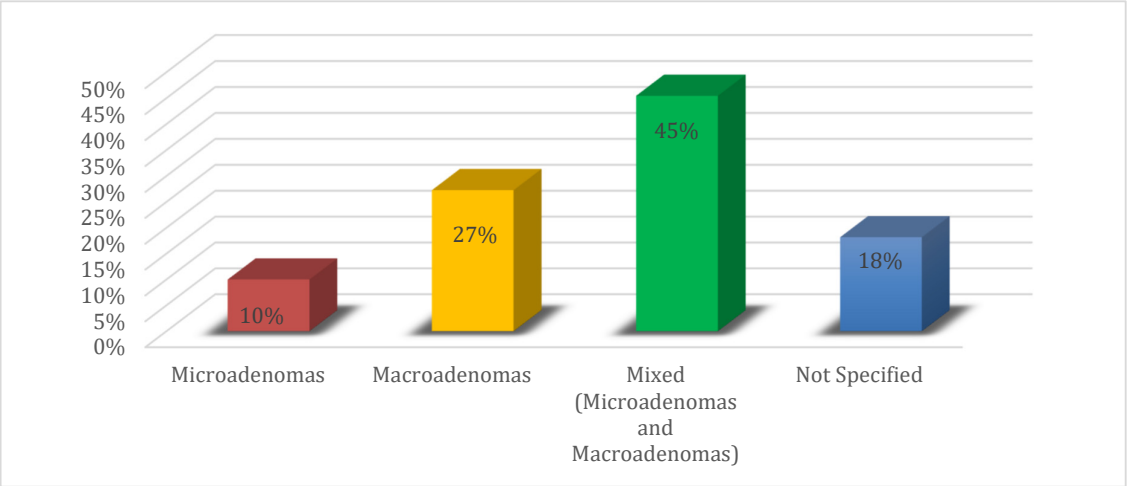

Figure 3. Distribution of Tumor Size Categories Among Studies

monly observed, followed by macroadenomas, with microadenomas being the least frequently reported. The data underscores the variability in tumor classification across different studies.

Table 3 presents the country-wise distribution of tumor types, highlighting the geographical spread of different adenoma classifications. Microadenomas are reported in studies from China (28). Macroadenomas are observed in research from France, Turkey, and Pakistan (23,25,26). The mixed category, which includes both microadenomas and macroadenomas, is seen in Italy, the UK, India, Turkey, and Thailand (22,24,29,30,32). Finally, cases with unspecified tumor types are documented in Georgia and India (27,31). This table emphasizes the global distribution of different tumor types, with particular countries contributing to various tumor classifications.

Table 4 outlines the primary treatments and treatment adjustments for hormonally active pituitary adenomas (HAPAs) in pregnant women. Dopamine agonists (DAs), including cabergoline and bromocriptine, are the most commonly used primary treatments. Adjustments during pregnancy involve stopping DAs upon pregnancy confirmation, with exceptions in two cases. In some situations, DAs are restarted or adjusted to control tumor progression or introduced after the first trimester to minimize fetal risks. In 28 pregnancies, DAs were discontinued, but six pregnancies continued treatment due to insufficient tumor reduction, and in 24 pregnancies, cabergoline was stopped. Surgical treatments are typically performed in the second trimester, with conservative management employed for stable cases. Combination therapy, such as bromocriptine and dydrogesterone, is continued until the first trimester or used up to 20 weeks in cases of recurrent pregnancy loss. Other treatments include evaluating macroprolactinemia and starting dopamine agonist therapy erroneously, along with monitoring variable responses to DAs in some patients.

Table 5 outlines the therapeutic management and monitoring approaches for hyperprolactinemia and prolactinomas. Dopamine agonist (DA) treatments, including cabergoline and bromocriptine, are commonly prescribed to normalize prolactin (PRL) levels and reduce tumor size before conception. Close monitoring is necessary for tumor-related symptoms, with adjustments to DA therapy made for symptomatic growth, and surgical intervention is considered in severe cases like pituitary apoplexy. Microadenomas are generally observed, given their low tumor growth risk, while macroadenomas require careful monitoring or treatment to prevent progression. Cabergoline is preferred over bromocriptine due to its superior effectiveness in normalizing PRL and reducing tumor size. Hormonal monitoring with bromocriptine helps normalize PRL levels and support the luteal phase. In cases of underlying neurological disorders, levodopa and dopamine

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Table 3. Countries' wise distribution of tumor types

Tumor Type	Country	References
Microadenomas	China	(28)
Macroadenomas	France, Turkey, Pakistan	(23,25,26)
Mixed (Microadenomas & Macroadenomas)	Italy, UK, India, Turkey, Thailand	(22,24,29,30,32)
Not Specified	Georgia, India	(27,31)

Table 4. Primary treatments and treatment adjustments in pregnancy

Primary Treatment	Treatment Adjustments in Pregnancy	References
Dopamine Agonists (Cabergoline and Bromocriptine)	- DA stopped upon pregnancy confirmation, except for two cases.	(22)
	- Restarting or adjusting DA doses-controlled tumor progression.	(23)
	- DAs started after the first trimester to minimize fetal risks.	(24)
	- DA was discontinued in 28 pregnancies; continued in 6 due to insufficient tumor reduction.	(25)
	- Cabergoline stopped in 24 pregnancies; continued in 7 with high risk of enlargement.	(29)
Surgical Treatment	- Surgery performed in the second trimester; conservative management for stable cases.	(28)
Combination Therapy	- Bromocriptine and dydrogesterone continued until the first trimester; dydrogesterone was used up to 20 weeks in recurrent pregnancy loss.	(27)
Others	- Macroprolactinemia assessed; dopamine agonist therapy started erroneously.	(32)
	- Variable response to dopamine agonists in 11 patients.	(30)
	- Cabergoline therapy (0.25 mg twice weekly for 4 weeks).	(31)

Table 5. Therapeutic management and monitoring approaches for hyperprolactinemia and prolactinomas

Group	Management and Monitoring Approaches	References
Dopamine Agonist (DA) Treatment & Monitoring	Acquiesced to international laws in cases of hyperprolactinemia; the goal of the therapy was to restore the level of PRL hormone and the tumor size before conception.	(22)
	Close monitoring for tumor-related symptoms; adjusted DA therapy for symptomatic growth; surgical intervention in severe cases (e.g., apoplexy).	(23)
	Observation for microadenomas with low tumor growth risk; careful monitoring or treatment for macroadenomas to prevent progression.	(24)
	Cabergoline is more effective than bromocriptine for prolactin normalization and tumor shrinkage; surgical intervention is required for selected resistant cases.	(26)
	Hormonal monitoring with bromocriptine for PRL normalization and luteal phase support with dydrogesterone.	(27)
	Levodopa and dopamine agonists are prescribed for underlying neurotransmitter disorder and hyperprolactinemia; MRI is used for follow-up monitoring.	(30)
Surgical & Neurosurgical Interventions	Multidisciplinary approach with pre- and post-operative hormonal and visual monitoring.	(28)
	Serum prolactin levels were monitored 3 months after delivery/lactation; MRI scans were taken after pregnancy/lactation.	(29)
Multidisciplinary & Comprehensive Care	Multidisciplinary monitoring during pregnancy	(25)
Specialized Monitoring & Follow-Up	Regular monitoring of prolactin levels and ovulation induction after normalization of menses.	(31)
	PEG test recommended distinguishing macroprolactinemia from true hyperprolactinemia to prevent unnecessary treatment.	(32)

agonists are used. Surgical and neurosurgical interventions follow a multidisciplinary approach, with pre- and post-operative hormonal and visual monitoring. Post-delivery, prolactin levels are monitored, and MRI scans are conducted after pregnancy and lactation. Regular monitoring of prolactin levels and ovulation induction occurs after menstrual normalization, and the PEG test is recommended to distinguish macroprolactinemia from true hyperprolactinemia.

Table 6 presents the pregnancy outcomes and complications in women with hyperprolactinemia and prolactinomas. A high success rate of deliveries was reported, with 82.7% pregnancies resulting in term deliveries and only two spontaneous abortions. Out of 41 pregnancies, 39 resulted in successful deliveries, with complications such as pituitary apoplexy, severe headaches, and visual defects. Tumor growth during pregnancy occurred in 19.6% of patients, though obstetric outcomes were generally comparable to those of the general population. The use of dopamine agonists like Cabergoline showed no significant adverse effects on pregnancy, although complications such as lactation impairment and gestational diabetes were noted in a few cases. Minor complications included pre-eclampsia, placental insufficiency, and threatened preterm labor. Visual or neurological symptoms were rare, but misdiagnosis of macroprolactinemia led to inappropriate treatment in some cases.

Discussion

The current systematic literature review (SLR) highlights a global distribution of 10 studies, with notable contributions from Italy, France, the UK, Turkey, Pakistan, Georgia, China, India, and Thailand. Study designs are diverse, with a predominance of observational, retrospective, cohort, and cross-sectional studies. Sample sizes range from single case reports to larger cohorts, such as 107 participants in a Pakistani retrospective study and 43 participants in an Italian observational study. Hormonally active pituitary adenomas (HAPAs), including microadenomas, macroadenomas, and mixed tumors, are widely studied, with a focus on prolactinomas and growth hormone-secreting adenomas. Methodologies such as sys-

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Table 6. Pregnancy outcomes and complications in hyperprolactinemia and prolactinomas

Group	Pregnancy Outcomes	Complications	References
Successful Deliveries with Minimal Complications	82.7% term deliveries; 2 spontaneous abortions.	Preeclampsia, gestational diabetes, placenta previa, fetal distress.	(22)
	39 out of 41 pregnancies resulted in successful deliveries.	Pituitary apoplexy, severe headaches, and visual defects.	(28)
Tumor Growth During Pregnancy	Obstetric outcomes are comparable to those of the general population.	Symptomatic tumor growth in 19.6% of patients, including pituitary apoplexy.	(23)
	80.6% delivered at term; 12.5% early pregnancy loss.	No tumor expansion or adverse events.	(29)
Impact of Dopamine Agonists & Pituitary Apoplexy	No significant adverse effects on pregnancy.	Lactation impairment, no major adverse effects from Cabergoline therapy.	(24,31)
	27 live births (79.4%); no stillbirths.	One case of gestational diabetes, CSF rhinorrhea, biochemical prolactin normalization in 79.4%.	(25,26)
Minor Pregnancy-Related Complications	85.42% vaginal deliveries; preeclampsia and placental insufficiency.	Threatened preterm labor, preeclampsia.	(27)
Visual or Neurological Symptoms & Hormone Regulation	No pregnancy outcomes reported.	Hypogonadism, menstrual irregularities, no visual symptoms, misdiagnosis of macroprolactinemia leading to inappropriate treatment.	(30,32)

tematic reviews and cross-sectional analyses are prevalent in these studies. Studies from China and Thailand cover both prolactinomas and other adenomas, while Georgia and India focus on hyperprolactinemia without specifying adenomas.

For prolactinomas, consistent with prior findings, a study underscores that prolactinomas constitute nearly half of all pituitary adenomas, with a notable portion diagnosed in males. Male prolactinomas are often larger and more invasive compared to those in females, necessitating multimodal treatment due to higher resistance to standard pharmacotherapy (33). This finding further emphasizes the gender-specific differences in the prevalence and progression of prolactinomas, underlining the need for tailored treatment strategies. On the other hand, growth hormone-secreting adenomas are less commonly studied but exhibit distinct characteristics. These tumors often present with acromegaly or gigantism, leading to unique challenges in both diagnosis and management. Growth hormone-secreting adenomas typically result in different clinical manifestations, including metabolic disturbances, joint issues, and excessive growth of bones and soft tissues, which must be managed differently from prolactinomas.

Another study reveals that the incidence rates and asymptomatic detection of prolactinomas appear to be increasing over time. Standardized incidence rates were 3.77 to 16.87 per 100,000 population, demonstrating linear expansion over time (R2=0.67). The mean overall standardized incidence rate was 10.1 per 100,000 population; the final point prevalence was 175.1 per 100,000 population (34). This trend indicates a growing recognition and diagnosis of prolactinomas, which could be attributed to advancements in diagnostic techniques and an increased awareness of the condition. Additionally, a consensus statement from the Pituitary Society provides evidence-based recommendations for managing prolactin-secreting adenomas. It emphasizes the importance of accurate diagnosis through imaging and biochemical evaluations, noting that elevated serum prolactin levels may result from conditions other than prolactinomas (35). This insight reinforces the necessity for a comprehensive diagnostic approach and highlights the importance of distinguishing prolactinomas from other potential causes of hyperprolactinemia.

For growth hormone-secreting adenomas, however, diagnosing acromegaly or gigantism requires additional hormonal evaluations, such as IGF-1 measurements, which can present distinct treatment challenges. In conclusion, the studies reviewed offer valuable insights into the global distribution and evolving understanding of pituitary adenomas, particularly prolactinomas and growth hormone-secreting adenomas. The diversity of research methodologies and findings underscores the complexity of diagnosing and managing these conditions, emphasizing the need for tailored and evidence-based treatment strategies.

Tumor Size Distribution

The current SLR emphasized the tumor size distribution across studies, with Mixed (Microadenomas & Macroadenomas) comprising 45% of the total, followed by Macroadenomas at 27% and Microadenomas at 10%, with Not Specified cases making up 18%. Tumor sizes range from microadenomas as small as 4.3 × 4.4 × 6.2 mm to macroadenomas exceeding 3.3 × 2.9 × 2.5 cm, with occasional suprasellar extension. Pregnancy often influences tumor growth, with size increases noted in 19.6% of patients. While macroadenomas dominate mean tumor sizes (around 2.1 ± 0.9 cm), post-treatment shrinkage was observed in a few studies. Similarly, another study shows that pregnancy can influence the growth of pituitary adenomas, particularly in cases of macroprolactinomas, and it indicates that symptomatic growth occurs in approximately 20-30% of macroprolactinoma cases during pregnancy, which aligns with the noted increases in size observed in some patients (36).

Additionally, a study shows that pituitary tumors exhibit diverse clinical presentations, ranging from hormonal dysfunction and mass-effect symptoms to rare conditions like pituitary apoplexy or hydrocephalus. Special considerations are essential for pituitary tumors (PTs) in pregnancy, childhood, and the elderly (37). Furthermore, a study shows that if a patient becomes pregnant while on treatment, the use of dopamine agonists is typically dis-

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continued, but close monitoring is essential to manage any potential complications arising from tumor growth or compression symptoms, indicating that proactive treatment and monitoring can mitigate risks associated with pituitary adenomas during pregnancy (38). Additionally, primary pituitary tumors, predominantly adenohypophysial adenomas, are the second most common CNS tumors and most prevalent in adolescents and young adults. Diagnosis leverages histopathology, immunohistochemistry, and neuroimaging. Challenges include detecting microadenomas and managing macroadenomas. Less common are Rathke pouch tumors (craniopharyngiomas) and rare neurohypophysial tumors (pituicytomas), each with distinct features (39).

A study focusing on the predictive value of cyst/tumor volume ratios found that larger tumor volumes correlate with higher proliferative potential, suggesting that preoperative imaging can be instrumental in planning surgical interventions (40). This aligns with findings that indicate a significant proportion of macroadenomas require surgical management due to their size and associated complications. Furthermore, a retrospective analysis indicated that the incidence of double pituitary adenomas remains low, yet they contribute valuable data on tumor size dynamics within this category (41). These studies collectively reinforce the understanding of tumor size distributions and their clinical implications in managing pituitary adenomas, suggesting a need for ongoing research into optimal diagnostic and treatment strategies tailored to tumor characteristics.

Global Tumor Type Distribution

The Current SLR summarizes the distribution of tumor types across countries. Microadenomas are predominantly studied in China, while Macroadenomas are reported in France, Turkey, and Pakistan. Mixed types, combining micro- and macroadenomas, are explored in Italy, the UK, India, Turkey, and Thailand. Some studies, conducted in Georgia and India, lack specific tumor size classification. This table highlights a comprehensive global research focus on prolactinomas and their classifications. Similarly, a study shows that the global prevalence of macroprolactinemia among hyperprolactinemia cases is 18.9%, with significant regional variability, like Africa (30.3%), the Americas (29.1%), Europe (17.5%), Eastern Mediterranean (13.9%), South-East Asia (12.7%), and Western Pacific (12.6%) (42).

Furthermore, a population-based study of 47,180 pituitary tumors from the SEER database (2004–2016) reveals an increasing incidence of pituitary adenomas, peaking in 2015. Typical adenomas showed better survival outcomes, influenced by younger age and smaller tumor size. Male and Black patients had poorer prognoses, highlighting demographic disparities and emphasizing the need for targeted interventions (43). These findings contrast with reports from other regions, where macroprolactinomas are more commonly observed in males (44). This suggests that gender-related factors may contribute to the frequency and prognosis of different types of prolactinomas, further emphasizing the importance of considering demographic factors in both clinical and research settings.

Treatment Strategies

According to the current SLR, the methods of treatment can be classified into the following categories: dopamine agonists, surgical treatment, conservative management therapy, several variants of combination therapy, and endoscopic techniques. Both Cabergoline and Bromocriptine, which are classified under dopamine agonists, were usually stopped during pregnancy but resumed when there was a symptom of tumor growth or introduced after the first trimester to minimize fetal risks. Surgical interventions, which were often carried out on a postpartum basis or in the second trimester, were reserved for the most severe complications such as pituitary apoplexy and visual defects. Inconsequential conditions were treated conservatively, while recurrent pregnancy loss was alleviated through the use of combination therapies, such as bromocriptine and dydrogesterone, continued until the first trimester or used up to 20 weeks. Resistant cases were managed through endoscopic and gamma knife surgery.

For growth hormone-secreting adenomas, surgery may be more aggressive, often involving transsphenoidal surgery for tumors with greater invasiveness or when pharmacological management with dopamine agonists is not effective. The table depicts personalized treatment approaches according to the rate of tumor growth and the likelihood of the woman being pregnant, with specific adjustments based on tumor progression and the use of dopamine agonists. In South Asia, particularly in Pakistan, prolactinomas are relatively rare, and many cases tend to resolve spontaneously after delivery, with approximately 75% of patients experiencing significant improvement postpartum. Additionally, Cabergoline has been found to be more effective than Bromocriptine in lowering serum prolactin levels and reducing tumor volume during pregnancy. This finding highlights the possibility of spontaneous tumor regression after childbirth and emphasizes the importance of ongoing monitoring during both pregnancy and the postpartum period (45).

Research indicates that both Cabergoline and Bromocriptine are crucial dopamine agonists used to treat prolactinomas. Among these, Cabergoline has shown higher resolution rates compared to Bromocriptine, especially when treatment is extended, and the tumor size is reduced. This therapy is effective in normalizing prolactin levels and regressing tumor size, which can improve fertility outcomes for women with hyperprolactinemia. The factors influencing this outcome include the length of treatment, whether normoprolactinemia is achieved, whether the tumor size is reduced, and whether dopamine agonists are tapered to low doses (46).

Typically, dopamine agonist treatment is paused once pregnancy occurs, as both Cabergoline and Bromocriptine cross the placenta. While dopamine agonists are the first-line treatment for prolactinomas, surgery or radiotherapy may be necessary for refractory cases. For aggressive or uncontrolled tumors, alternative therapies, such as temozolomide, hormonal treatments, and cytotoxic drugs, have been employed. Emerging treatments, including

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mTOR inhibitors, tyrosine kinase inhibitors, and immunotherapy, show promise, though evidence is still limited (47). On the other hand, DAs should be resumed if symptoms indicating tumor growth appear during the prenatal period (48).

Recent literature normalizes the use of bromocriptine during pregnancy, as there was no statistically significant increase in rates of miscarriage, along with some birth defects among the sample versus the general population (49). There have also been mentions of cabergoline working and being well tolerated in pregnancy, and as such, in some clinical situations, it is preferred (50,51). With conservative approaches, patients with mild microprolactinomas are only followed expectantly. They are monitored, and at regular intervals, checks are conducted for any change in tumor growth or symptoms. Meanwhile, in patients with pregnancy loss due to prolactinomas that became recurrent, medication and management strategies to boost fertility may assist the patients (52).

The current review also includes dopamine agonist (DA) treatment, such as cabergoline and bromocriptine, followed by close monitoring of tumor growth using MRI to assess tumor progression and ensure tumor reduction. Severe manifestations were treated with transsphenoidal surgery and other neurosurgical procedures. Symptom management and fetal protection were possible as a result of multidisciplinary care, while a low risk of tumor growth during pregnancy was sustained by conservative management. Specific and trimester-related hormonal monitoring, along with dydrogesterone, ensured appropriate surveillance. Patient-centered lifestyle and behavioral changes formed an integral part of therapeutic approaches. Patients received dopamine agonists and, in some cases, surgical interventions, which marked a comprehensive care paradigm.

The changes emphasize dopamine agonist therapy, multidisciplinary care, conservative management, and hormonal monitoring. Additionally, references to MRI monitoring, transsphenoidal surgery, and patient-centered approaches reflect the findings from the study. Another study confirms that dopamine agonists remain the cornerstone of prolactinoma treatment. Other literature suggests cabergoline is more effective than bromocriptine in ensuring normal prolactin levels and reducing tumor size. For example, a review found that cabergoline has a high rate of success in biochemical remission and recovery of gonadal function (54). However, challenges such as side effects and treatment resistance necessitate ongoing research into alternative therapies (55).

Surgical options, particularly transsphenoidal surgery, are increasingly being recognized as viable first-line treatments for certain patients with microprolactinomas or well-circumscribed macroprolactinomas. Surgical treatment for prolactinomas shows similar remission rates to dopamine agonists (DAs) but offers higher drug-free remission for microadenomas and macroadenomas without cavernous invasion. For macroadenomas with cavernous invasion, surgery combined with DA therapy yields higher remission rates. Individual treatment should consider tumor characteristics, as DA therapy is not always first-line (56). The evolving perspective on surgery reflects its potential to minimize the need for long-term DA treatment, especially in younger patients. The management of prolactinomas has expanded its understanding to be multidisciplinary so as to achieve better outcomes for the patients. Besides medications and surgeries, this also involves activities such as educating the patient or behavioral change. It is encouraged that less dangerous tumors are treated with active surveillance techniques, but all risks are managed through trimester-based MRIs and glucocorticoid replacements as required (57).

Moving on, more recent literature mentions the use of somatostatin analogues and tyrosine kinase inhibitors for patients who cannot tolerate the DAs, which are regarded as the first line of treatment (58).

Pregnancy and Outcomes

The current SLR presents the results of pregnancies; successful deliveries with minimal complications have been recorded, irrespective of the issues described. Problems of lesser concern were mastitis and leiomyomas, while the symptomatic growth of the tumor led to visual impairment, headaches, and compression over the optic chiasm. The effects of therapy using dopamine agonists turned out to be safe, with infrequent adverse effects like lactation impairment. There were some cases where the mildest symptoms attributed to pituitary apoplexy or even hypopituitarism were noted. A sundry range of issues, like preeclampsia and gestational diabetes, were said to be pregnancy-related issues. Although some pregnancies were affected by visual or neurological symptoms, the final results were still encouraging. Hormonal treatment ensured that it became possible to get pregnant and deliver a baby, while the management of moderate galactorrhea and misdiagnosis of macroprolactinemia leading to inappropriate treatment was hesitant.

Consistently, another study has also identified the pregnancy results among women with prolactin-secreting tumors and more commonly with hyperprolactinemia, which have improved over time, and complications have existed. Successful deliveries are frequently reported, with minor complications such as mastitis and leiomyomas being common. Further along, problems of tumor expansion that can impair vision and cause headaches, as well as compression of the optic chiasm, need to be taken into consideration (59). The use of dopamine agonists has been reassuring, as they effectively reduce prolactin levels while also addressing metabolic concerns. However, some less common side effects, like the inability to lactate, have been noted. Rare but extreme events such as pituitary apoplexy or hypopituitarism have also occurred (60). Moreover, hyperprolactinemia, a common cause of infertility and recurrent pregnancy loss, has been shown to increase miscarriage rates significantly compared to women without this condition (61). This supports the understanding that elevated prolactin levels can impede reproductive success.

Additionally, research indicates that treating hyperprolactinemia has a positive impact on pregnancy and perinatal outcomes. Hyperprolactinemia, often caused by factors

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such as medications or seller/parasellar masses, is a prevalent endocrinological disorder that requires careful diagnosis. This includes assessing for macroprolactin and considering the hook effect. Treatment typically focuses on restoring gonadal function and preventing osteoporosis, but emerging evidence also suggests that it may affect metabolism, bone health, and immune function (62, 63).

Another study focused on IVF outcomes in patients with varying prolactin levels, suggesting that mildly elevated prolactin levels may actually correlate with better pregnancy outcomes in assisted reproductive technologies (64). In addition, although complications like preeclampsia and gestational diabetes were observed in pregnancies with hyperprolactinemia, they were considered minor. Elevated prolactin levels were associated with reduced insulin and beta-cell function as well as increased insulin sensitivity during the post-partum period, though the exact causality remains unclear. Visual or neurological symptoms, though reported, did not significantly affect the overall positive pregnancy outcomes (65). Thus, while there are challenges associated with hyperprolactinemia during pregnancy, including visual and neurological symptoms and the potential for complications like mastitis and preeclampsia, the overall success in achieving pregnancies and delivering healthy babies remains high, with management strategies such as dopamine agonist therapy playing a critical role.

Conclusion

The current systematic review highlights the significant global research efforts addressing the challenges of managing pituitary adenomas and hyperprolactinemia during pregnancy. The study underscores the worldwide contributions, with diverse methodologies ranging from observational studies to randomized controlled trials. Countries like Italy, France, Turkey, Pakistan, China, and Thailand lead in research volume, while studies from India and Thailand focus on both prolactinomas and other adenomas. The inclusion of large cohorts, such as a Pakistani retrospective study (107 participants), contrasts with smaller sample sizes, such as the study from India (20 participants), reflecting the variability in study designs and sample sizes.

The study delves into the classification and geographical distribution of tumor sizes and types. Mixed tumors represent the most studied tumor type, comprising 45% of the cases, followed by macroadenomas (27%) and microadenomas (10%). Tumor sizes varied widely, from microadenomas as small as 4.3 × 4.4 × 6.2 mm to macroadenomas exceeding 3.3 × 2.9 × 2.5 cm. Pregnancy often influenced tumor behavior, with notable growth during gestation, such as size increases from 1 cm to 2 cm or 11 mm to 19 mm. Microadenomas were primarily the focus of the research conducted in China, Pakistan, and India, whereas macroadenomas were studied largely in France, Turkey, and Pakistan. This pattern of investigating a mix of cases is observed in Italy, the UK, and Thailand, illustrating that the focus of research is distributed worldwide.

The study also highlights the main lines of management and the modifications made during pregnancy. Most tumoral cases used dopaminergic therapy with either cabergoline or bromocriptine, usually stopping them when pregnancy was confirmed, but adjusting or recommencing them when there was symptomatic progression of the tumor. Such patients were managed surgically in cases of severe complications, such as transsphenoidal resection for cases showing neurological signs, and in the second trimester or after delivery. The disease was treated conservatively or with combination therapy that included bromocriptine, accompanied by dydrogesterone during cases of pregnancy loss, which points to individualized management strategies.

In relation to therapeutic management and monitoring methods, the present work demonstrates a multi-faceted approach in order to achieve optimum results. The aim of the dopamine agonist therapy was the normalization of prolactin levels and reduction of tumor mass, assisted by consistent MR imaging and hormonal checks. The patients who required surgery were managed with respect to multidisciplinary measures to address troublesome symptoms and regain hormonal and visual functions. Those requiring a watchful eye approach were placed under this management strategy, while other cases followed different follow-up schedules, such as trimesters of MRIs to assess the risks of tumor growth. Education for those patients and changes in lifestyle were crucial in enhancing compliance with treatment, while options considered in post-surgical settings included gamma knife radiosurgery and replacement of thyroid hormones.

Lastly, the study focuses on the outcomes and complications of pregnancy. Most women had healthy newborns without many complications related to delivery. Symptomatic complications such as visual field defects, pituitary apoplexy, and severe headaches were, however, caused by the tumor's growth during pregnancy. The use of dopamine agonists was largely risk-free with minimal side effects such as lactation deficiency or gestational diabetes. Delivery or having a baby was common in many cases, although women endured hypertension and diabetes while pregnant. Most reproductive outcomes and hormonal management had a positive effect on the success rates of conceiving and delivering children, although there were times when a wrong diagnosis led to a mismanagement of treatment. This thorough research overview demonstrates the efficacy of the typical individual contribution and the contribution of several specialists to the supervision of pituitary adenomas with hormonal activity during the gestational period, where the health of the mother and the fetus is considered alongside the tumor.

Research limitations or gaps

This study on hormonally active pituitary adenomas and pregnancy has multiple shortcomings. First, the difference in the study's designs, which ranged from single case reports to large retrospective studies, creates heterogeneity that impedes the ability to draw uniform conclusions. Moreover, the skewed geographical representation of the studies, with a few countries such as Italy, France, Turkey, Pakistan, India, and China making the most contributions, may not be representative of global patients and health

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systems. Many of the included studies rely on observational data that is often biased, and more often than not, the data does not include control groups, thus questioning the strength of the findings. Furthermore, much of the literature is limited by a lack of information relating to tumor activity during pregnancy and maternal as well as fetal long-term outcomes. The tumor type distribution, such as the predominance of mixed tumors (45%) and macroadenomas (27%), is not well represented across all studies, which can lead to potential underrepresentation or overrepresentation of certain tumor categories. The lack of uniform diagnostic and treatment protocols complicates the comparison of results, particularly regarding the use of dopamine agonists and their adjustments in pregnancy, where there are variations in stopping or restarting therapies. Finally, small sample sizes in several studies hinder the generalizability of conclusions, emphasizing the need for larger, multicenter prospective studies to provide comprehensive insights into this complex condition.

Authors' Contributions

Ainur Dossanova was responsible for conceptualizing the study, defining the inclusion and exclusion criteria, and conducting the database search. Shahlo Abduzhabarova coordinated the screening and quality assessment processes and contributed to data synthesis. Rimma Bazarbekova analyzed the clinical and endocrinological implications of the included studies. Svetlana Kazaryan contributed to the interpretation of obstetric outcomes and critically revised the final manuscript. All authors participated in the drafting of the manuscript, approved the final version, and are accountable for the accuracy and integrity of the entire data. Data analyzed in this study are openly accessible through the databases cited (Web of Science, Scopus, PubMed, CORE, and Google Scholar) and are referenced accordingly in the article. No unpublished data were used.

Ethical Considerations

Not applicable.

Acknowledgment

Not applicable.

Conflict of Interests

The authors declare that they have no competing interests.

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