UNDER PEER REVIEW

Study Protocol

Prolactinoma and Pregnancy: A Systematic Review Protocol

Abstract

Introduction: Prolactinomas are the most common pituitary tumors, especially affecting women in their 3rd and 4th decades, being an important cause of irregular menses and infertility. Fertility can be restored, turning pregnancy possible, in most of the cases, mainly microprolactinomas, with clinical treatment (dopamine agonist (DA)) and eventually neurosurgery. Although literature data point to safety in maternal and fetal outcomes, especially regarding symptomatic tumor growth and DA fetal exposure, there is no meta-analysis. Ideal length of DA treatment in macroprolactinomas, abortion rate and neuropsychological development are important gaps in the management of DA- induced pregnancies. Additionally, previous radiotherapy and neurosurgery main impact on maternal-fetal outcomes.

Objective: This systematic review aims to evaluate the association between pregnancy and prolactinoma with respect to the control of prolactinoma and fetal/maternal outcomes.

Methods: This review will be conducted according to the Joanna Briggs Institute methodology for systematic reviews of etiology and risk. We will focus on observational studies that included pregnant women with prolactinoma. The outcomes will be prolactinoma control, preterm birth, maternal adverse events related to the use of DA, worsening of preexisting diabetes or the development of gestational diabetes, spontaneous miscarriage, frequency of breastfeeding, perinatal mortality, low birthweight, small for gestational age, congenital malformations, tumor size, headache, visual impairment, apoplexy, neurosurgery, clinical/biochemical recurrence of prolactinomas/hyperprolactinemia after pregnancy. Embase, Medline, LILACS, and CENTRAL will be our source databases. Two reviewers independently will select the studies, extract data and critically appraise the eligible studies. We will use Stata Statistical Software 17 to plot similar outcomes in at least two studies in meta-analyses. For controlled studies, relative risks will be calculated with 95% confidence intervals (CIs) as an estimate of the exposure effect, and for continuous data we will calculated means and standard deviations, and the mean differences will be calculated with respective 95% CIs. For uncontrolled studies we will perform proportional meta-analyses. The protocol of this review was registered in the PROSPERO database (registration number: CRD42021283757).

Conclusions: The results of this review can help in the management of prolactinoma in women before, during and after pregnancy.

Keywords

Prolactinoma; Pituitary Neoplasms; Pregnancy; Dopamine agonists; Neurosurgery; Radiotherapy.

Introduction

Among the functioning pituitary adenomas, prolactinomas are the most common, accounting for more than half of all pituitary tumors, with a higher prevalence in young women of childbearing age [1-3].

Prolactinoma causes hypersecretion of prolactin (PRL), which generates hypogonadotropic hypogonadism, mainly by inhibiting both pulsatile secretion of GnRH and gonadal steroidogenesis. This can cause menstrual irregularity and amenorrhea in women, and sexual dysfunction, infertility, and loss of bone mineral mass in both sexes [4-5]. PRL hypersecretion also promotes changes in sperm viability and quantity, as well as luteal phase shortening, anovulation, oligomenorrhea, and amenorrhea [2]. Thus, hyperprolactinemia is an important cause of infertility in both men and women. However, the development of clinical and surgical therapies, in particular the administration of dopamine agonists, has made pregnancy possible in most cases [6].

Dopamine agonists, such as bromocriptine and cabergoline, are considered a first-line treatment of prolactinoma, and promote hyperprolactinemia reversal and tumor reduction, enabling conception and pregnancy [6]. Treatment with dopamine agonists is quite effective in reducing prolactin levels, and the restoration of fertility can be immediate, even before the first normal menstruation. Although more pregnancy safety data are available for bromocriptine, both cabergoline and bromocriptine appear to be safe during pregnancy, with no associated increased risk of miscarriage and preterm delivery [7-8]. However, it is recommended to discontinue these medications after the confirmation of pregnancy in most pregnant women. The exceptions are cases of macroprolactinoma, whose management is individualized and depends on the size of the lesion, degree of aggressiveness, and average time of treatment prior to pregnancy. However, the diagnosis of pregnancy sometimes occurs late, and it is also

known that many patients become pregnant during dopamine agonist treatment without fertility planning. Because of this the embryo can be exposed to the drug during the initial period of its development, which is an important phase of embryogenesis [6,9]. Thus, there are questions about the safety of these drugs during pregnancy and their possible repercussions on fetal development.

Tumor cells in patients with prolactinoma express estrogen receptors, and during pregnancy, tumor growth may occur due to high estrogen concentrations and consequent lactotroph hyperplasia [6,10]. Furthermore, the physiological increase in the pituitary gland is highlighted by the recruitment and differentiation of somatotrophs into lactotrophs [2,11,12]. Therefore, the greatest concern for pregnant women with prolactinomas is tumor growth during pregnancy, especially in women with macroprolactinomas [11,13]. Previous studies reported that the average risk of symptomatic growth in a macroprolactinoma is 27.9%, while that in patients with microprolactinoma is 2.2%. Signs and symptoms related to mass effect, such as visual field changes and headache, appear as a result of adenoma growth [6,11].

In view of the difficulties caused by prolactinoma that are observed in clinical practice, especially for women who become pregnant spontaneously, it is important to clarify the association between pregnancy and prolactinoma in terms of disease control, fetal/maternal outcomes and regarding the safety of drugs used to control prolactinoma during pregnancy. Although some relevant information in this topic has been published, the evidence has not been systematically synthesized.

Thus, the objective of the present study is to perform a systematic review evaluating the association between prolactinoma and pregnancy with respect to pituitary disease control and maternal and fetal outcomes.

Review question

The question that will be addressed in this review is how pregnancy in prolactinoma influences the control of prolactinoma and fetal/maternal outcomes.

Methods

The proposed systematic review will be conducted in accordance with the Joanna Briggs Institute methodology for systematic reviews of etiology and risk (Chapter 7:

Systematic reviews of etiology and risk) [14]. The protocol of this review was registered with the PROSPERO database (registration number: CRD42021283757) and was developed following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.

Inclusion Criteria

Participants

This review will consider studies that included pregnant women over 18 years of age who were diagnosed with prolactinoma before or during the first trimester of pregnancy.

Exposure of Interest

The exposure of interest is prolactinoma on pregnancy outcomes as well as pregnancy on prolactinoma control. Prolactinoma diagnosis will be considered as a single measurement of serum prolactin level in patients with pituitary tumors, excluding medication use, renal failure, hypothyroidism, and parasellar tumors.

Outcomes

This review will consider studies that include the following outcomes:

1- Main outcomes:

Maternal primary outcomes:

a) PRL control (measured by clinical symptoms and MRI, if necessary) before and postpartum

b) Preterm birth

c) Worsening of preexisting diabetes or the development of gestational diabetes

d) Maternal adverse events related to the use of dopamine agonists at conception or during pregnancy

e) Frequency of breastfeeding

Fetal/newborn primary outcomes

a) Perinatal mortality (including stillbirth/fetal death and neonatal death)

b) Low birthweight (less than 2500 g)

2 - Additional outcomes:

Maternal secondary outcomes

a) Tumor size before, during, and postpartum (measured using magnetic resonance imaging [MRI])

b) Headache

e) Spontaneous miscarriage

f) Apoplexy

g) Clinical/biochemical recurrence of prolactinomas/hyperprolactinemia after pregnancy

h) Frequency of neurosurgery

Fetal and newborn secondary outcomes

a) Small-for-gestational age

b) Congenital malformations

Types of studies

This review will consider observational studies, including prospective and retrospective cohort studies, cross sectional, and case series (at least three participants) studies.

Exclusion Criteria

Case reports and case series with less than three participants will be excluded.

Search strategy

The search strategy aims to identify published and unpublished studies. A preliminary search of PubMed was performed to identify articles on this topic. The search strategy, including all the identified keywords and index terms, will be adapted for each included information source. The reference lists of all studies selected for critical appraisal will be screened for additional eligible studies. There will be no language or year restrictions.

Information sources

Search strategies have been applied to the following electronic health databases: Embase (by Elsevier, 1980–2022), Medline (by PubMed, 1966–2022), Latin American and Caribbean Health Sciences Literature (by Virtual Health Library, 1982–2022), and controlled clinical trials of the Cochrane Collaboration (Cochrane Central Register of Controlled Trials).

We have used the following index terms and synonyms: prolactinoma and pregnancy. Language and year restrictions will not be considered in this study. References of relevant primary and secondary studies will be searched to identify additional eligible studies. The draft PubMed and EMBASE search strategies are included in Appendix I. The following databases will also be investigated for eligible studies: Trip database; SCOPUS, Web of Science; and CINAHL.

Study selection

All identified citations will be collated and uploaded into the bibliographic software EndNote X9 /2019, and duplicates will be removed. Titles and abstracts will then be screened by two independent reviewers (DBB and LSA) using the free web application Rayyan QCRI. The full texts of the selected citations will be assessed in detail against the inclusion criteria by two independent reviewers. The reasons for the exclusion of full text studies will be recorded and reported in the systematic review. Disagreements between reviewers at each stage of the study selection process will be resolved through discussion or by a third reviewer (VSNN). The results of the search will be reported in full in the final systematic review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [15] flow diagram.

Assessment of methodological quality

Eligible studies will be critically appraised by two independent reviewers (DBB and LSA) at the study level or methodological quality in the review, using standardized critical appraisal instruments from the Joanna Briggs Institute for cohort, cross sectional and case series studies. Authors of papers will be contacted to request missing or additional data for clarification where required. Any disagreements that arise will be resolved through discussion or by a third reviewer. The results of the critical appraisal will be reported in narrative form and in a table.

All studies, regardless of their methodological quality, will undergo data extraction and synthesis (where possible). If possible, the results of critical appraisal will be incorporated into sensibility analysis using a meta-analysis approach.

Data Extraction

Data will be extracted from the papers included in the review using a standardized data extraction tool by two independent reviewers (DBB and LSA). The extracted data will include specific details about exposure (time of prolactinoma, control status before pregnancy, age, type of treatment, macro-or microadenoma), study design, number of patients, number of pregnant women and outcome results.

Disagreements between the reviewers will be resolved through discussion or by a third reviewer. Authors of papers will be contacted to request missing or additional data if needed.

Data Synthesis

Similar outcomes in at least two studies will be plotted in the meta-analysis using Stata Statistical Software 17 (Stata Statistical Software: Release 17. College Station, TX, USA). In controlled studies, for dichotomous data, relative risk will be calculated with 95% confidence intervals (CIs) as an estimate of the exposure effect. Continuous data will be expressed as means and standard deviations, and the differences between the means with 95% CIs will be used as an estimate of the exposure effect. A random effect model will be used for the meta-analysis. Narrative synthesis will be provided when quantitative synthesis is not appropriate.

For non-controlled studies, prolactinoma control and tumor size pre- and postpartum will be compared, to calculate the overall frequencies of dichotomous data, proportional meta-analyses will be performed. We will use the updated command "metaprop_one" and fit the logistic normal random effects model to the data. The number of events will be used as the numerator and the number of pregnancies and newborns will be used as the denominator for maternal and fetal outcomes, respectively. In order not to overestimate the control of prolactinoma and not to underestimate tumor growth during pregnancy, for these outcomes, we will use as the denominator the number of pregnancies in which these outcomes were evaluated

In the presence of evidence synthesis from controlled studies, the quality of evidence of the effect of exposure will be assessed according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodological guidelines [16].

CONCLUSION

Results of this review can help in the management of prolactinoma in pregnant women.

Ethical approval

As no primary data collection will be undertaken, no formal ethical assessment is required by the authors' institution.

References

1. Samperi I, Lithgow K, Karavitaki N. Hyperprolactinemia. J Clin Med. 2019;8:2203.
2. Glezer A, Bronstein MD. Prolactinomas. Endocrinol Metab Clin N Am. 2015;44(1):71-8.
3. Vilar l, et al. Questões polêmicas no manejo da hiperprolactinemia e prolactinomas - uma visão geral do Departamento de Neuroendocrinologia da Sociedade Brasileira de Endocrinologia e Metabolismo. Arq Endocrinol Metab. 2018;62(2):236–63.
4. Marshall JC, Dalkin AC, Haisenleder DJ, Griffin ML, Kelch RP. GNRH pulses - the regulators of human reproduction. Trans Am Clin Climatol Assoc. 1993;104:31-46.
5. Kleinberg DL, Noel GL, Frantz AG. Galactorrhea: a study of 235 cases, including 48 with pituitary tumors. N Engl J Med. 1977; 296(11):589-600.
6. Melmed S, et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society Clinical Practice guideline. J Clin Endocrinol Metab. 2011; 96(2):273-88.
7. Mancini T, Casanueva F, Giustina A. Hyperprolactinemia and prolactinomas. Endocrinol Metab Clin N Am. 2008;37:67-99.
8. Casanueva F, Molitch ME, Schlechte JA, et al. Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. Clin Endocrinol. 2006;65:265-73.

9. Glezer A, Bronstein MD. Prolactinomas in pregnancy: considerations before conception and during pregnancy. Pituitary. 2020;23(1):65-9.
10. Pichon MF, Bression D, Peillon F, Milgrom E. Estrogen receptors in human pituitary adenomas. J Clin Endocrinol Metab. 1980;51(4):897–902.
11. Bronstein MD, Paraiba DB, Jallad RS. Management of pituitary tumors in pregnancy. Nat Rev Endocrinol. 2011;7(5):301-10.
12. Huang W, Molitch ME. Pituitary tumors in pregnancy. Endocrinol Metab Clin. 2019; 48(3):569-81.
13. Molitch ME. Prolactinoma in pregnancy. Best Pract Res Clin Endocrinol Metab. 2011; 25(6):885-96.
14. Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, et al. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (Editors). Joanna Briggs Institute Reviewer Manual. The Joanna Briggs Institute, 2017. Available from https://reviewersmanual.joannabriggs.org/
15. Moher D, Liberati A, Tetzlaff J, Altman DG; Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009; 6(7):e1000097.
16. Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. BMJ (Clinical research ed). 2016; 353: i2089.

Supplementary file

Appendix I: Search strategy

Pubmed = ("Prolactinoma"[Mesh] OR (Prolactinomas) OR (Lactotroph Adenoma) OR (Adenoma, Lactotroph) OR (Adenomas, Lactotroph) OR (Lactotroph Adenomas) OR (Prolactinoma, Familial) OR (PRL-Secreting Pituitary Adenoma) OR (PRL Secreting Pituitary Adenoma) OR (PRL-Secreting Pituitary Adenomas) OR (Pituitary Adenoma, PRL-Secreting) OR (Pituitary Adenomas, PRL-Secreting) OR (Prolactin-Producing Pituitary Adenoma) OR (Pituitary Adenoma, Prolactin-Producing) OR (Pituitary Adenomas, Prolactin-Producing) OR (Prolactin Producing Pituitary Adenoma) OR (Prolactin-Producing Pituitary Adenomas) OR (Prolactin-Secreting Pituitary Adenoma) OR (Prolactin Secreting Pituitary Adenoma) OR (Adenoma, Prolactin-Secreting, Pituitary) OR (Pituitary Adenoma, Prolactin-Secreting) OR (Pituitary Adenoma, Prolactin Secreting) OR (Pituitary Adenomas, Prolactin-Secreting) OR (Prolactin-Secreting Pituitary Adenomas) OR (Microprolactinoma) OR (Microprolactinomas) OR (Macroprolactinoma) OR (Macroprolactinomas)) AND ("Pregnancy"[Mesh] OR (Pregnancies) OR (Gestation) OR (Pregnant women) OR (Pregnant) OR (Lactating women) OR (Maternal iodine intake) OR (Postpartum) OR (Pregnant patient)) = 715

Embase = ('prolactinoma'/exp OR 'lactotroph adenoma'/exp OR 'lactotroph adenomas'/exp OR 'macroprolactinoma'/exp OR 'macroprolactinomas'/exp OR 'microprolactinoma'/exp OR 'microprolactinomas'/exp OR 'prl producing adenoma'/exp OR 'prl producing adenomas'/exp OR 'prl producing pituitary adenoma'/exp OR 'prl producing pituitary adenomas'/exp OR 'prl producing pituitary tumor'/exp OR 'prl producing pituitary tumors'/exp OR 'prl producing pituitary tumour'/exp OR 'prl producing pituitary tumours'/exp OR 'prl producing tumor'/exp OR 'prl producing tumors'/exp OR 'prl producing tumour'/exp OR 'prl producing tumours'/exp OR 'prl secreting adenoma'/exp OR 'prl secreting adenomas'/exp OR 'prl secreting pituitary adenoma'/exp OR 'prl secreting pituitary tumor'/exp OR 'prl secreting pituitary tumors'/exp OR 'prl secreting pituitary tumour'/exp OR 'prl secreting pituitary tumours'/exp OR 'prl secreting tumor'/exp OR 'prl secreting tumour'/exp OR 'prl secreting tumours'/exp OR 'prolactin producing adenoma'/exp OR 'prolactin producing adenomas'/exp OR 'prolactin producing pituitary adenoma'/exp OR 'prolactin producing pituitary adenomas'/exp OR 'prolactin producing pituitary tumor'/exp OR 'prolactin producing pituitary tumors'/exp OR 'prolactin producing pituitary tumour'/exp OR 'prolactin producing pituitary tumours'/exp OR 'prolactin producing tumor'/exp OR 'prolactin producing tumors'/exp OR 'prolactin producing tumour'/exp OR 'prolactin producing tumours'/exp OR 'prolactin secreting adenoma'/exp OR 'prolactin secreting adenomas'/exp OR 'prolactin secreting pituitary adenoma'/exp OR 'prolactin secreting pituitary adenomas'/exp OR 'prolactin secreting pituitary tumor'/exp OR 'prolactin secreting pituitary tumors'/exp OR 'prolactin secreting pituitary tumour'/exp OR 'prolactin secreting pituitary tumours'/exp OR 'prolactin secreting tumor'/exp OR 'prolactin secreting tumors'/exp OR 'prolactin secreting tumour'/exp

OR 'prolactin secreting tumours'/exp OR 'prolactinomas'/exp) AND [embase]/lim AND ('pregnancy'/exp OR 'child bearing'/exp OR 'childbearing'/exp OR 'gestation'/exp OR 'gravidity'/exp OR 'intrauterine pregnancy'/exp OR 'labor presentation'/exp OR 'labour presentation'/exp OR 'pregnancy maintenance'/exp OR 'pregnancy trimesters'/exp) AND [embase]/lim = 479