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Acromegaly and Pregnancy: A Systematic Review Protocol

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Authors' contributions

This work was carried out in collaboration among all authors. Authors VSNN, DBB and TOFO conceptualized and design the study. Authors VSNN, DBB, TOFO and CLB draft the manuscript protocol. Authors VSNN, DBB, TOFO and CLB draft the manuscript protocol, critically revised it and manuscript submitted. All authors read and approved the final manuscript.

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Study Protocol

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ABSTRACT

Introduction: Although the association between acromegaly and pregnancy has been studied, recent evidence synthesis is lacking.
Objective: To evaluate the association between acromegaly and pregnancy in terms of disease control and newborn/maternal outcomes.
Methods: We will perform a systematic review according to Joanna Briggs Institute methodology for systematic reviews of etiology and risk. We will include studies with pregnant women, over 18 years old, diagnosed with acromegaly before or during the first trimester of pregnancy. Studies with pregnancy before acromegaly diagnosis will be excluded. We will consider cohort and case-control studies, and case series (at least 3 participants). Maternal primary outcomes will be acromegaly control, preterm birth, presence of diabetes, hypertension and/or eclampsia, and frequency of abortion. Newborn primary outcomes will be perinatal mortality and low birthweight. General and adaptive search strategies have been created for the Embase, Medline, LILACS, and CENTRAL

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databases. Two independent reviewers will assess eligibility of the studies, extract data, and evaluate their risk of bias. For dichotomous data, effect estimates will be calculated using relative risk with 95% confidence intervals (CIs). Continuous data will be expressed as means and standard deviation (SD) for each study, and the mean difference will be calculated with respective 95% CIs. For non-controlled studies, maternal outcomes will be compared pre- and postpartum, and for abortion frequency and newborn outcomes, we will perform proportional meta-analysis. **Conclusion:** We hope that the results of this review can help the management of pregnant women with acromegaly.

Keywords: Acromegaly; pituitary neoplasms; pregnancy.

1. INTRODUCTION

Acromegaly is related to the risk of development of comorbidities in pregnancy, such as diabetes, hypertension and cardiac disease, in addition to potential obstetric and fetal complications [1]. Conversely, hormonal effects of gestation may lead to increased lesion and/or hyperplasia of the pituitary lactotrophs, leading to optic chiasmal compression and visual field loss [2]. Several factors may influence the clinical and hormonal activity of acromegaly during pregnancy, including the concentration of grow hormone (GH) derived from the pituitary adenoma, placental GH levels (which increase after mid-gestation), and the increase in estrogen levels (hence resistance to GH, which is highly variable among patients) [3].

Although some case reports have shown deterioration of acromegaly during pregnancy,[4,5] several studies have reported that conception with acromegaly is generally safe from a maternal and fetal perspective [6]. Additionally, Dias et al., in a prospective study published in 2013, showed both biochemical and clinical stability in acromegaly during pregnancy, especially in women with effectively treated tumors prior to conception [7]. Jallad et al. in a cohort of women with acromegaly showed that out of 15 pregnant women followed without any medical or surgical treatment, 13 exhibited normal Insulin-like Growth Factor 1 (IGF-1) levels [8]. However, both these observational studies showed that uncontrolled acromegaly before pregnancy was associated to an increased risk of worsening comorbidities.

Regarding treatment of acromegaly during pregnancy, drug therapy may be discontinued for most patients [7,8]. However, in patients with worsening disease activity, treatment should be reconsidered. According to the guidelines of the Endocrine Society published in 2014, discontinuation of long-acting somatostatin analogues or pegvisomant is recommended within two months of the estimated pregnancy date and if necessary, use of short-term octreotide until conception. During pregnancy, drug therapy is recommended only for control of tumor growth and/or headaches [9]. Nevertheless, patients with aggressive disease may require personalized treatment, such as surgery or oral medications, during pregnancy and lactation [10]. Based on data from pregnant women with prolactinoma, cabergoline has been shown to be safe for the fetus [11]. This reduces concerns for the use of this drug in pregnant women with acromegaly [10].

This lessens concern for its use in patients with acromegaly.

Difficulties are observed in the clinical practice of acromegaly and pregnancy, because many patients become pregnant during medication therapy and without any fertility planning. Therefore, it is particularly important to clarify the association between pregnancy and acromegaly in terms of disease control and fetal/maternal outcomes. Although some studies have published relevant information in this topic, no recent evidence synthesis has been performed. A preliminary search in PROSPERO, PubMed, the Cochrane Database of Systematic Reviews, and the *JBI Database of Systematic Reviews and Implementation Reports* was conducted, and we identified a published systematic review of case and series reports in acromegaly and pregnancy [12]. However, it was published in 2012, only PubMed was used as data source, and since then at least four new studies with larger cohorts have been published [6-8,13].

Thus, the objective of this review was to evaluate the association between pregnancy and acromegaly in terms of disease control and fetal/maternal outcomes. Our main hypothesis is that pregnancy improves control of acromegaly, except for patients with uncontrolled acromegaly

before pregnancy. In addition, acromegaly might be safe on maternal and neonatal outcomes.

1.1 Review Question

How does pregnancy in acromegaly influence the control of acromegaly and fetal/maternal outcomes?

2. 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 has been registered with the PROSPERO database (registration number: CRD42020151416) and was developed following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols [15].

2.1 Inclusion Criteria

2.1.1 Participants

This review will consider studies that included pregnant women, over 18 years old, diagnosed with acromegaly before or during the first trimester of pregnancy.

2.1.2 Exposure of interest

The exposure of interest will be acromegaly on pregnancy outcomes, as well as pregnancy on acromegaly control. We will consider acromegaly diagnosis as an elevated serum IGF-1 level, associated to lack of GH suppression below 1 µg/L following documented hyperglycemia during an oral glucose load [9].

2.1.3 Outcomes

This review will consider studies that included the following outcomes:

1- Main outcomes:

Maternal primary outcomes:

a) Acromegaly control (measured according to random GH and IGF1 levels)
b) Preterm birth
c) Presence of gestational diabetes (according to fasting glucose and glucose tolerance test, also known as oral glucose tolerance test)
d) Presence of hypertension and/or eclampsia (based on blood pressure). Preeclampsia diagnosis includes high blood pressure and one or more of the following complications after the 20th week of pregnancy: Protein in the urine (proteinuria); low platelet count; impaired liver function; signs of kidney problems other than protein in the urine; pulmonary edema; new-onset headaches or visual disturbances.

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 and during pregnancy and postpartum (based on Magnetic Resonance Imaging - MRI)
b) Headache
c) Spontaneous miscarriage
d) Acromegaly comorbidity control, such as hypertension and diabetes diagnosed before pregnancy.
e) Maternal adverse effects for patients in drug therapy for acromegaly

Fetal/newborn secondary outcomes:

a) Small-for-gestational age
b) Congenital anomalies
c) Fetal macrosomia

2.1.4 Types of studies

This review will consider observational studies including prospective and retrospective cohort studies, case-control studies, and case series (at least 3 participants).

2.2 Exclusion Criteria

We will exclude case reports and case series with less than 3 participants.

2.3 Search Strategy

The search strategy will aim to identify both published and unpublished studies. A preliminary search in PubMed was performed to identify articles on the topic. The search strategy,

including all identified keywords and index terms, will be adapted for each included information source. The reference list of all studies selected for critical appraisal will be screened for additional eligible studies. There are no language and year restrictions.

2.4 Information Sources

Search strategies have been applied to the following electronic health databases: Embase (by Elsevier, 1980–2020), Medline (by PubMed, 1966–2020), Latin American and Caribbean Health Sciences Literature (by Virtual Health Library, 1982–2020), and Controlled Clinical Trials of the Cochrane Collaboration (Cochrane Central Register of Controlled Trials). We have used the following index terms and their synonyms: acromegaly, gigantism, gh-secreting pituitary adenoma, pregnancy. Language or year restrictions will not be considered in this study. References of relevant primary or secondary studies will be searched to identify additional eligible studies. Draft PubMed and Embase search strategies are included in appendix I.

The following databases will also be interrogated for eligible studies: Trip database, SCOPUS, Web of Science, CINAHL. We will also search for studies on ClinicalTrials.gov and gray literature through conferences, published abstracts, and dissertations.

2.5 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 TOFO) using the free web application Rayyan QCRI [16]. Full texts of selected citations will be assessed in detail against the inclusion criteria by two independent reviewers. Reasons for 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) flow diagram [17].

2.6 Assessment of Methodological Quality

Eligible studies will be critically appraised by two independent reviewers (DBB and TOFO) using standardized critical appraisal instruments from the Joanna Briggs Institute for cohort, case-control and case-series studies. Authors of papers will be contacted to request missing or additional data for clarification, if needed. Disagreements will be resolved through discussion, or by a third reviewer. The results of critical appraisal will be reported in narrative form and in tables.

All studies, regardless of the results 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 on meta-analysis approach.

2.7 Data Extraction

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

Disagreements between 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.

2.8 Data Synthesis

Similar outcomes in at least two studies will be plotted in the meta-analysis using the Stata Statistical Software 16 (*Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC). For dichotomous data, the relative risk will be calculated with 95% confidence intervals (CIs) as the estimate of the intervention effect. Continuous data will be expressed as means and standard deviation, and the differences between means with 95% CIs will be used as an estimate of intervention effect. A random-effects model will be used for the meta-analysis. When quantitative synthesis is not appropriate, a narrative synthesis will be provided.

For non-controlled studies, acromegaly control and tumor size will be compared pre- and postpartum, and frequency of gestational diabetes, hypertension/eclampsia, abortion, preterm birth, and newborn outcomes will be evaluated with proportional meta-analyses. In the presence of evidence synthesis from controlled studies, the quality of the evidence of the exposure's effect estimate will be assessed according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodological guidelines [18].

3. CONCLUSION

We hope that the results of this review can help the management of pregnant women with acromegaly

ETHICAL APPROVAL

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

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Chanson P, Vialon M, Caron P. An update on clinical care for pregnant women with acromegaly. Expert Rev Endocrinol Metab. 2019;14(2):85-96.
2. Goluboff LG, Ezrin C. Effect of pregnancy on the somatotroph and the prolactin cell of the human adenohypophysis. J Clin Endocrinol Metab. 1969;29(12):1533-8.
3. Muhammad A, Neggers SJ, van der Lely AJ. Pregnancy and acromegaly. Pituitary. 2017;20(1):179-84.
4. O'Herlihy C. Pregnancy in an acromegalic after bromocriptine therapy. Ir J Med Sci. 1980;149(7):281-2.
5. Montini M, Pagani G, Gianola D, Pagani MD, Piolini R, Camboni MG. Acromegaly and primary amenorrhea: ovulation and pregnancy induced by SMS 201-995 and bromocriptine. J Endocrinol Invest. 1990;13(2):193.
6. Hannon AM, O'Shea T, Thompson CA, Hannon MJ, Dineen R, Khattak A, et al. Pregnancy in acromegaly is safe and is associated with improvements in IGF-1 concentrations. Eur J Endocrinol. 2019;180(4):K21-K9.
7. Dias M, Boguszewski C, Gadelha M, Kasuki L, Musolino N, Vieira JG, et al. Acromegaly and pregnancy: a prospective study. Eur J Endocrinol. 2014;170(2):301-10.
8. Jallad RS, Shimon I, Fraenkel M, Medvedovsky V, Akirov A, Duarte FH, et al. Outcome of pregnancies in a large cohort of women with acromegaly. Clin Endocrinol (Oxf). 2018;88(6):896-907.
9. Katznelson L, Laws ER, Jr., Melmed S, Molitch ME, Murad MH, Utz A, et al. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(11):3933-51.
10. Abucham J, Bronstein MD, Dias ML. Management of endocrine disease: Acromegaly and pregnancy: a contemporary review. Eur J Endocrinol. 2017;177(1):R1-R12.
11. Sant' Anna BG, Musolino NRC, Gadelha MR, Marques C, Castro M, Elias PCL, et al. A Brazilian multicentre study evaluating pregnancies induced by cabergoline in patients harboring prolactinomas. Pituitary. 2020;23(2):120-8.
12. Cheng S, Grasso L, Martinez-Orozco JA, Al-Agha R, Pivonello R, Colao A, et al. Pregnancy in acromegaly: Experience from two referral centers and systematic review of the literature. Clinical Endocrinology. 2012;76(2):264-71.
13. Karaca Z, Yarman S, Ozbas I, Kadioglu P, Akturk M, Kilicli F, et al. How does pregnancy affect the patients with pituitary adenomas: a study on 113 pregnancies from Turkey. J Endocrinol Invest. 2018;41(1):129-41.
14. Moola S MZ, 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's Manual: The Joanna Briggs Institute; 2017. Available:https://reviewersmanual.joannabriggs.org/
15. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred

reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ (Clinical research ed). 2015;350:g7647.

16. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210.
17. 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.
18. 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.

APPENDIXES

Appendix I: Search strategy

PubMed = (("Acromegaly"[Mesh] OR (Somatotropin Hypersecretion Syndrome (Acromegaly)) OR (Hypersecretion Syndrome, Somatotropin (Acromegaly)) OR (Hypersecretion Syndromes, Somatotropin (Acromegaly)) OR (Somatotropin Hypersecretion Syndromes (Acromegaly)) OR (Syndrome, Somatotropin Hypersecretion (Acromegaly)) OR (Syndromes, Somatotropin Hypersecretion (Acromegaly)) OR (Inappropriate GH Secretion Syndrome (Acromegaly)) OR (Inappropriate Growth Hormone Secretion Syndrome (Acromegaly)) OR "Growth Hormone-Secreting Pituitary Adenoma"[Mesh] OR (Pituitary Growth Hormone-Secreting Adenoma) OR (Pituitary Growth Hormone Secreting Adenoma) OR (Pituitary Adenoma, GH-Secreting) OR (Pituitary Adenoma, GH Secreting) OR (Somatotroph Adenoma) OR (Adenoma, Somatotroph) OR (Adenomas, Somatotroph) OR (Somatotroph Adenomas) OR (GH-Secreting Pituitary Adenoma) OR (GH Secreting Pituitary Adenoma) OR (GH-Secreting Pituitary Adenomas) OR (Pituitary Adenomas, GH-Secreting) OR (Growth Hormone Tumor*) OR "Gigantism"[Mesh] OR (Pituitary Gigantism) OR (Gigantism, Pituitary))) AND ("Pregnancy"[Mesh] OR (Pregnancies) OR (Gestation) OR (Pregnant women) OR Pregnant) OR (Lactating women) OR (Maternal iodine intake) OR (Postpartum) OR (Pregnant patient)) = 525

EMBASE = ('pregnancy'/exp OR 'child bearing' OR 'childbearing' OR 'gestation' OR 'gravidity' OR 'intrauterine pregnancy' OR 'labor presentation' OR 'labour presentation' OR 'pregnancy maintenance' OR 'pregnancy trimesters') AND ('acromegaly'/exp OR 'acromegalia' OR 'acromegalism' OR 'akromegalia' OR 'megalakria' OR 'gigantism'/exp OR 'giant man' OR 'hypersomatotrophy' OR 'man, giant' OR (('growth hormone secreting adenoma'/exp OR 'gh producing adenoma' OR 'gh producing adenomas' OR 'gh producing pituitary adenoma' OR 'gh producing pituitary adenomas' OR 'gh producing pituitary tumor' OR 'gh producing pituitary tumors' OR 'gh producing pituitary tumour' OR 'gh producing pituitary tumours' OR 'gh producing tumor' OR 'gh producing tumors' OR 'gh producing tumour' OR 'gh producing tumours' OR 'gh secreting adenoma' OR 'gh secreting adenomas' OR 'gh secreting pituitary adenoma' OR 'gh secreting pituitary adenomas' OR 'gh secreting pituitary tumor' OR 'gh secreting pituitary tumors' OR 'gh secreting pituitary tumour' OR 'gh secreting pituitary tumours' OR 'gh secreting tumor' OR 'gh secreting tumors' OR 'gh secreting tumour' OR 'gh secreting tumours' OR 'growth hormone-secreting pituitary adenoma' OR 'growth hormone producing adenoma' OR 'growth hormone producing adenomas' OR 'growth hormone producing pituitary adenoma' OR 'growth hormone producing pituitary adenomas' OR 'growth hormone producing pituitary tumor' OR 'growth hormone producing pituitary tumors' OR 'growth hormone producing pituitary tumour' OR 'growth hormone producing pituitary tumours' OR 'growth hormone producing tumor' OR 'growth hormone producing tumors' OR 'growth hormone secreting adenomas' OR 'growth hormone secreting pituitary adenoma' OR 'growth hormone secreting pituitary adenomas' OR 'growth hormone secreting pituitary tumor' OR 'growth hormone secreting pituitary tumors' OR 'growth hormone secreting pituitary tumour' OR 'growth hormone secreting pituitary tumours' OR 'growth hormone secreting tumor' OR 'growth hormone secreting tumors' OR 'growth hormone secreting tumour' OR 'growth hormone secreting tumours' OR 'somatotroph adenoma' OR 'somatotroph adenomas' OR 'somatotropinoma' OR 'somatotropinomas' OR growth) AND hormone AND tumor*)) AND ([adult]/lim OR [middle aged]/lim OR [young adult]/lim) AND [embase]/lim = 290

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