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Review article

Effects of depression pharmacotherapy in fertility treatment on conception, birth, and neonatal health: A systematic review

Leo E. Akioyamen [a,b,*], Hersimren Minhas [c,d], Alison C. Holloway [e], Valerie H. Taylor [a,f], Noel O. Akioyamen [g], Diana Sherifali [b,h]

[a] Faculty of Medicine, University of Toronto, Toronto, ON M5S 1A8, Canada
[b] School of Nursing, McMaster University, Hamilton, ON L8N 3Z5, Canada
[c] College of Health Professions, Rosalind Franklin University of Medicine and Science, North Chicago, IL 60064, USA
[d] Faculty of Science, McMaster University, Hamilton, ON L8S 4M1, Canada
[e] Department of Obstetrics & Gynecology, McMaster University, Hamilton, ON L8S 4K1, Canada
[f] Division of Women's Mental Health, Women's College Research Institute, Toronto, ON M5G 1N8, Canada
[g] Arthur Labatt Family School of Nursing, Western University, London, ON N6A 5C1, Canada
[h] Diabetes Care and Research Program, Hamilton Health Sciences, Hamilton, ON L8N 3Z5, Canada

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ABSTRACT

Objectives: While antidepressant medications are currently used during conception, gestation and post-partum, considerable uncertainty exists regarding the benefits and harms conferred to mothers and their offspring. A significant body of evidence has focused on antidepressant use during pregnancy and post-partum. However, it is difficult to know if this translates to specific populations. Women receiving treatment for infertility are especially vulnerable to symptoms of depression and adverse perinatal outcomes. This systematic review aimed to determine the effects of antidepressants taken during the perinatal period by women receiving fertility treatment on conception, birth, and long-term maternal and child health outcomes.
Methods: We searched MEDLINE, EMBASE, CINAHL, the Cochrane Library, PsycINFO, ProQuest Dissertation & Theses, and Pubmed databases from January 1950 to November 2015. Articles were screened for inclusion independently by two reviewers. Studies were included if they enrolled women of reproductive age exposed to pharmacotherapy for depression and infertility at any point during the perinatal period.
Results: A total of 8587 unique citations, and 83 full-text articles were reviewed. Of these, two randomized controlled trials and two retrospective chart reviews were included in the narrative synthesis. While most studies reported on assisted reproduction processes and birth outcomes, none examined long-term impacts on maternal–child health. The few included studies did not find that antidepressant use by women receiving fertility therapy impacted gamete quality or pregnancy success.
Conclusions: Currently, no studies address whether pharmacotherapy for the treatment of depression in women undergoing assisted reproduction affects their health or that of their offspring long-term. It appears that much like antidepressant use in fertile women, there are risks associated with both antidepressant use and untreated depression. Decisions regarding the treatment of depression should be made taking into account clinical presentation and illness severity. Given the complexities of conducting research in this population, future research should attempt to leverage health registry data, to increase sample sizes and follow mothers and children longitudinally.

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1. Introduction

For multiple reasons, the inability to conceive is experienced as a stressful situation causing great emotional suffering. These include the initial and progressive feelings of loss of control over one's life and reproductive functions, feelings of alienation and stigmatization, the sometimes significant life-style adjustments necessitated by fertility treatment and blame of one's self for infertility and therapeutic failures [1,2]. The prevalence of depressive symptoms among infertile women has been reported as being twice as high as that of fertile women [3,

* Corresponding author at: Faculty of Medicine, University of Toronto, Mississauga Academy of Medicine, 3359 Mississauga Road – Terrence Donnelly Health Sciences Complex, Mississauga, ON L5L 1C6, Canada.
E-mail addresses: sele.akioyamen@mail.utoronto.ca (L.E. Akioyamen), minhash@mcmaster.ca (H. Minhas), hollow@mcmaster.ca (A.C. Holloway), valerie.taylor@wchospital.ca (V.H. Taylor), oakioyam@uwo.ca (N.O. Akioyamen), dsherif@mcmaster.ca (D. Sherifali).

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4]. Further, levels of distress and anxiety in infertile women persist over extended periods of time, tending to increase as treatment intensifies and the duration of treatment lengthens [1,5]. Importantly, when infertile women were compared to those with cancer, hypertension, myocardial infarction, chronic pain, and HIV-positive status, depression and anxiety scores differed significantly from only those with chronic pain [6].

Psychological interventions such as cognitive behavioral therapy, remain the first-line treatment for infertile women exhibiting mild-to-moderate depressive symptoms [5]. Recent evidence suggests that these approaches are effective at reducing stress and anxiety levels in infertile women [1,5]. Despite this, the use of pharmacological interventions for depression and anxiety in infertile women remains high as current guidelines recommend antidepressants with or without concurrent psychotherapy as first line treatment for more severe depression presentations in pregnancy [7]. The prevalence of antidepressant use has been reported to comprise as much as 4 and 11% of women undergoing infertility treatment [8]. One review of electronic medical records found that only a third of infertile women taking antidepressants acknowledged using these medications when queried by healthcare providers [8], suggesting that the use of these medications may be more pervasive.

More than half of infertile women receiving antidepressants prior to conception are reported to take these medications following parturition and presumably, during pregnancy [9]. All psychotropic medications studied to date have been shown to cross the placenta, be present in amniotic fluid, and enter human breast milk, making it likely for offspring of treated women to be exposed to these medications in utero and postnatally [10]. Pharmacological therapies for depression have been linked to adverse outcomes for mothers and children. Women receiving antidepressants during pregnancy have been said to face an increased risk of post-partum hemorrhage and anemia [11,12]. Their children were also more likely to be delivered preterm (i.e., under 37 weeks gestation) and with a low birth-weight (i.e., under 2500 g) [13]. Adding to the complexity, however, is evidence linking adverse neonatal outcomes to untreated depression as well [14].

Assisted reproduction also presents with significant maternal-child risk. Compared to women not receiving fertility treatment, those undergoing treatment are at increased risk for placental abnormalities, including placenta abruptio and placenta previa [15]. These adverse obstetric outcomes are present even in singleton pregnancies [16] and may compound existing risks of preterm and low birth-weight delivery [15]. Preterm birth and low birth-weight – whose risks are increased with treatment for fertility or depression – are considered to be the leading causes of neonatal, infant, and childhood morbidity, mortality, and neurodevelopmental impairment worldwide [13,17–19]. Further, associated aberrant postnatal growth patterns have been linked to increased cardiovascular and metabolic risk in adulthood for exposed individuals [20–23]. Antidepressant use has also been more directly associated with metabolic derangements in exposed children and adults [24–26]. Thus, there is increasing concern about the short and long-term antenatal effects of exposure to antidepressants in women treated for infertility and their children.

While a significant body of evidence has focused on the impact of antidepressant use during pregnancy and the post-partum period, it is difficult to know how this translates to specific populations. It may be that much as with use in unassisted reproduction, there are risks associated with both illness and illness treatment and it is important to be able to articulate risks appropriately. We therefore sought to systematically review the literature regarding the long-term impacts of concurrent perinatal exposure to pharmacotherapies for infertility and depression. Specifically, we aimed to explore the impacts of antidepressant use while receiving fertility treatment on: (a) maternal health outcomes; (b) birth and related outcomes; and (c) growth and metabolic outcomes in exposed infants and children.

2. Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) consensus statement in this study's design and implementation [27]. The protocol for the review was registered with the PROSPERO International Prospective Register of Systematic Reviews (CRD42014014986).

2.1. Search strategy

Under the guidance of a health sciences librarian with experience supporting systematic reviews, we used validated strategies to search MEDLINE, EMBASE, CINAHL, PsycINFO, the Cochrane Library, the ProQuest Dissertation & Theses database, and Pubmed (for publications ahead of print). Databases were searched for published, peer-reviewed literature by combining terms related to the use of oral and injectable fertility medications and in vitro fertilization (IVF) with pharmacologic treatments for depression and terms related to depression and infertility (Fig. 1). Results were limited to human studies published between the year 1950 and August 2014, with an updated search run on 12 November 2015 (Appendix 1). Only English-language studies were included due to limitations of the review team. We reviewed reference lists of all included articles and relevant literature reviews, systematic reviews and meta-analyses for additional eligible studies.

2.2. Study selection

Pairs of reviewers independently evaluated candidate titles and abstracts and full-texts using standardized forms. Disagreements between reviewers were resolved by discussion to consensus. Studies were eligible if they included women of childbearing age receiving oral or injectable fertility pharmacotherapy as well as depression medication at any point during the perinatal period. We defined the perinatal period as encompassing the period prior to conception, throughout gestation, or within six months post-partum. The great specificity of the research question – driven by combinatorial treatment exposure, the outcomes of interest, and risks generally posed by the disease area – made it likely that few controlled intervention studies would be found eligible. Thus, our eligibility criteria were tailored to facilitate the inclusion of any study designs with the potential to yield reasonably valid effect estimates with regard to the exposure (see Box 1). Our outcomes of interest were related to birth, and maternal and offspring health:

- *Birth outcomes*: pregnancy rates, birth rates, spontaneous abortion, preterm birth, low birth weight, being small for gestational age, pre-eclampsia, eclampsia, HELLP syndrome, congenital malformations.
- *Maternal health outcomes*: depression prevalence, depression severity, weight, body mass index (BMI), blood pressure, body fat percentage, lean body mass, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, fasting glucose, random blood glucose, fasting insulin, glycated hemoglobin.

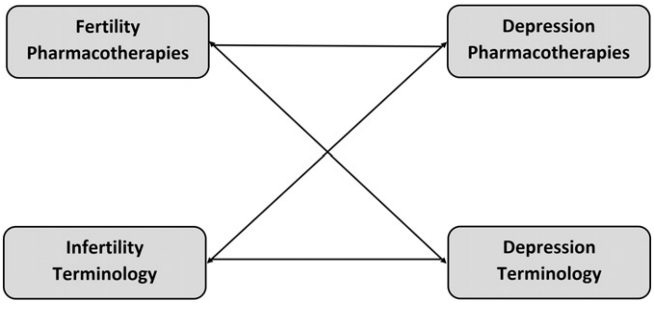

Fig. 1. Search terms for systematic review of depression pharmacotherapy in assisted reproduction.

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