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# Risperidone as a galactagogue of choice in peripartum: A concise review

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## Abstract:

Human lactation is a dynamic physiological process that produces a complex biological fluid that provides nutritive and nonnutritive factors for an optimal child growth and well-being. Several factors play a formidable role in maternal breast milk production with respect to quality, and quantity, which will adequately sustain the child for at least the first 6 months after delivery. Evidence has shown majority of new mothers who wished to immediately commence exclusive breastfeeding after birth as recommended by the WHO, are unable to initiate lactation immediately. In view of this lactation insufficiency, health-care personnel have not only been campaigning on appropriate breastfeeding education but also offer early lactation support such as encouraging liberal fluid intake, dietary modifications, and in a worst-case scenario, administering agents/drugs such as galactagogue. Orthodox galactagogues in current use are either hormonal or antipsychotics; most of them have relative efficacy and safety limitations. Risperidone is an atypical antipsychotic which has been used for decades with established safety in lactating mothers and the highest propensity to induce galactorrhoea as a secondary effect when compared to other antipsychotics that are currently being used as galactagogues. We call the attention of the medical community in conducting further researches on its possible adoption as a galactagogue, using this review as an insight.

## Keywords:

Galactagogues, lactation, low breast milk, peripartum, risperidone

## Introduction

Breast milk is a complex biological fluid that plays both nutritive and immune-protective roles for an optimal growth of the newborn. Exclusive breastfeeding for the first 6 months of life and supplementary breastfeeding till the second birthday or beyond have been advocated by the World Health Organization as a gold standard nutritional approach for adequate infant growth.<sup>[1]</sup> Well-breastfed infants are conferred some degree of immunity against numerous early-life, potentially fatal infections of the gastrointestinal, respiratory, and genitourinary systems. Breastfeeding also protects infants against numerous noncommunicable neonatal diseases such as necrotizing enterocolitis, chronic lung

disease, retinopathy, intellectual disability, pediatric neoplasms as well as later-life illnesses such as bronchial asthma, allergy, diabetes mellitus, and obesity.<sup>[2]</sup> Lactating mothers are more confident, psychologically stable, and at lower risk of breast, ovarian, endometrial, and other gynecological neoplasms.<sup>[3]</sup>

Successful lactation requires extensive breast tissue expansion and differentiation during pregnancy, followed by the ability to produce sufficient amounts of milk after birth. Low volume of milk production or lactation insufficiency is among the several reasons why new mothers do not commence or continue exclusive breastfeeding.<sup>[4]</sup> Exclusive breastfeeding completion also depends on copious breast milk production, and various methods have been used to increase the volume of breast milk including a trial of herbal galactagogue.<sup>[5]</sup>

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Several pharmacological galactagogues (domperidone, metoclopramide, sulpiride, oxytocin, metformin, growth hormone, thyrotrophin-releasing hormone, and recombinant human prolactin) had been tried with suboptimal response, hence an expectation of a more efficacious, tolerable pharmacological galactagogue is being yearned for.<sup>[3]</sup> Therefore, in this review, we highlight a novel human milk production booster that should be a future research focus.

### Relationship Mechanism of Action of Risperidone and Lactation

Most atypical antipsychotics exert their therapeutic effect via the dopaminergic and serotonergic blockage.<sup>[6]</sup> Risperidone is a novel atypical antipsychotic that shows a high affinity for D<sub>2</sub> receptors via the tuberoinfundibular route,<sup>[6]</sup> a neuroendocrine pathway of which inhibition of dopamine production results in a reciprocal hyperprolactinemia,<sup>[7]</sup> and subsequently galactorrhea in females<sup>[8]</sup> which is considered a secondary or an adverse effect when the medication is primarily used as antipsychotic therapy.

### Secondary Effect of a Medication in Treatment of an Illness

Evidence has shown that clinicians do employ the secondary benefit of a medication that is supposedly a primary therapeutic indication or drug of choice for another illness,<sup>[9]</sup> and similarly, some drugs used in another field of medicine were by chance discovered to be useful and effective in another specialty.<sup>[10]</sup> Several examples are bound in published literatures. Antihypertensive medications such as calcium channel blockers, angiotensin-converting enzyme inhibitors, and beta-adrenergic blockers have secondary benefits in the treatment of migraine headaches.<sup>[11,12]</sup> The side effect of beta-adrenergic blockers – bradycardia, a drug for managing hypertension, is employed primarily in the treatment of palpitation in patients with task-specific anxiety<sup>[13]</sup> and thyrotoxicosis.<sup>[14]</sup> There is an increasing use of some anti-epileptic agents for nonepileptic disorders.<sup>[15,16]</sup>

It is interesting to note that the first-ever orthodox antipsychotic medication (chlorpromazine) was first introduced to the pharmacopeia in the 1950s as a serendipity when trying to synthesize preanesthetic medications from other phenothiazine groups and haloperidol (with other sister butyrophenones) when trying to synthesize analgesics from opioid derivatives.<sup>[17]</sup> Prior to this era of psychopharmacological revolution, *Rauwolfia serpentina* had been a known phytomedicinal product employed locally in Nigeria as an antipsychotic.<sup>[18]</sup> In summary, there are significant relationships between

drug side effects and therapeutic indications probably for a different disease entity, of which low-dose risperidone can serve as a galactagogue when need be.

### Physiology of Human Lactation and Breastfeeding

Functional lactation is mediated by a complex interplay of neurological, endocrine, physical, and psychological factors.<sup>[19]</sup> Mammary epithelial cells undergo differentiation into secretory lactocytes by the mid-late trimester under the influence of placenta-derived gonadotrophins (human chorionic gonadotrophins, estrogen, and progesterone) which are counter-regulatory to prolactin.<sup>[20]</sup> The lactotrophs synthesize the components of human milk under the direct or indirect influence of metabolic hormones such as glucocorticoids, insulin, insulin-like growth factor 1, growth hormone, and thyroid hormones. The sudden drop in the level of the circulating gonadotrophins following the placental expulsion results in a high level of circulating prolactin and consequently leads to copious milk secretion.<sup>[17,18]</sup> Oxytocin facilitates milk ejection from the mammary duct by initiating the contraction of alveolar myoepithelial cells. In addition to endogenous factors, exogenous stimuli, such as baby's cry, stress, and infant's suckle, lead to the inhibition of dopamine (anti-dopaminergism), increase the secretion of prolactin, and hence increase the secretion of breast milk.

In essence, optimal lactation is determined by the sufficiency of mammary glandular tissue, functionality of neuroendocrine system, and regularity of breast emptying. The neuroendocrine control of lactation may be affected by the following but not limited to maternal psychological status, drug and alcohol use, and medical comorbidities.<sup>[4]</sup> Establishment and maintenance of adequate lactation in mothers of preterm neonate usually pose challenges due to physiological immaturity of the breast as well as the neonate.

### Safety of Risperidone during Breastfeeding

The safety of using antipsychotics generally while breastfeeding is still very controversial and to conduct robust randomized clinical trials to evaluate the risks of antipsychotics for mother and child is ethically difficult.<sup>[21,22]</sup> The drug plasma level of antipsychotics not more than 10% of the mother's therapeutic range is acceptably safe.<sup>[23]</sup> However, risperidone is among the studied second-generation antipsychotics that is relatively safe and tolerable during breastfeeding.<sup>[24,25]</sup> Two nursing mothers that took a daily dose of oral 4 and 6 mg risperidone, respectively, were followed up for at least 9 months and no adverse effect was observed in their exclusively breastfed babies.<sup>[25]</sup>

## Conclusion

Various alternative approaches have been suggested in the management of hypogalactia and agalactia. Wet nursing is a practice that has been known since antiquity in addressing this health challenge or similar situations such as severe maternal illness that hinder breastfeeding or in a case of maternal death. Donor breast/milk banking and/or pasteurization of donor human milk are other options; however, the risk of disease transmission and not retaining some natural nutritional components are their respective limitations. Breast milk substitutes are not recommended in low- and middle-income countries due to its nonaffordability and its composition is not an absolute match for human milk as well.

We recommend robust interventional studies using risperidone as a galactagogue in postpartum mothers with hypogalactia or agalactia.

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## Conflicts of interest

There are no conflicts of interest.

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