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REVIEW

Polycystic ovarian syndrome and low milk supply: Is insulin resistance the missing link?

Lora Stanka Kirigin Biloš

Department of Endocrinology, Diabetes and Metabolic Diseases "Mladen Sekso", University Hospital Center "Sestre Milosrdnice", University of Zagreb Medical School, Vinogradska Cesta 29, 10000 Zagreb, Croatia

Corresponding author:

Lora Stanka Kirigin Biloš, Department of Endocrinology, Diabetes and Metabolic Diseases "Mladen Sekso", University Hospital Center "Sestre Milosrdnice", University of Zagreb Medical School, Zagreb, Croatia, Phone: +91-919326983, e-mail: lora.s.kirigin@gmail.com

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Abstract

Despite the known maternal and infant benefits of breastfeeding, only about two-fifths of infants are exclusively breastfed for the first 6 months of life, with low milk supply among the most commonly cited reasons for breastfeeding cessation. Although anecdotal reports from lactation consultants indicate that polycystic ovarian syndrome (PCOS) interferes with lactation, very few studies have examined this relationship, and the association between PCOS and lactation dysfunction remains poorly understood. Moreover, studies have reported conflicting results when examining breastfeeding success in women with PCOS, and divergence of the PCOS phenotype may be responsible for the heterogeneous results to date. Specifically, insulin resistance may have an aggravating or even essential role in the pathogenesis of low milk supply. Recently, protein tyrosine phosphatase, receptor type, F has been identified as a potential biomarker linking insulin resistance with insufficient milk supply. Accordingly, interventions targeting insulin action have been recognized as potentially promising strategies toward the treatment of lactation dysfunction. This review will highlight studies linking PCOS with low milk supply and explore potential mechanisms that contribute to lactation dysfunction in these women.

Key words: Insulin resistance; lactation; low milk supply; polycystic ovarian syndrome

1. Introduction

Breastfeeding provides many benefits to both mother and child, which is why the World Health Organization (WHO) and the American Academy of Pediatrics recommend exclusive breastfeeding for the first 6 months of life with continued breastfeeding until at least 1 year [1,2]. However, only about two-fifths of infants worldwide are exclusively breastfed for the first 6 months of life [3], with low milk supply accounting for the majority of breastfeeding cessation [4,5].

Polycystic ovarian syndrome (PCOS) is characterized by chronic anovulation, hyperandrogenism, and polycystic ovarian morphology [6]. The cause of PCOS is multifactorial and not fully understood, with a combination of genetic and environmental factors the likely culprit [7]. Several hormonal alterations are found in women with PCOS including ovarian hyperandrogenism and insulin-resistant hyperinsulinism.

Breastfeeding involves a complex interplay of several hormones, many of which are disordered in women with PCOS, and these hormonal alterations may interfere with mammatogenesis, lactogenesis, or galactopoiesis [8]. Anecdotal reports from lactation consultants indicate that PCOS interferes with lactation; however, very few studies have examined this relationship. This is surprising considering the high prevalence of PCOS among women of childbearing age [9] and the known benefits of breastfeeding [10]. Furthermore, due to advances in reproductive technology, more and more women with PCOS have successful pregnancies, with little known about the effect, it will have on lactation.

Studies have reported conflicting results when examining breastfeeding success in women with PCOS (Table 1) [11,12], and the contribution of PCOS to lactation difficulties remains poorly understood. The first study to suggest a potential link between PCOS and low milk supply was a case report that described three women with PCOS who failed to breastfeed [8]. Later, in a case-control study, Vanky et al. reported somewhat reduced breastfeeding rates in women with PCOS in the early postpartum period [11].

Insulin resistance and obesity are negatively associated with lactation [13-15], and because women with PCOS have an increased risk for both obesity and insulin resistance [6,16], this may contribute to their lactation difficulties. In addition, hyperandrogenism, as well as alterations in estrogen, progesterone, and prolactin metabolism may also be involved in the pathogenesis [17].

Although the association and mechanism behind PCOS and low milk supply still need to be elucidated, clinicians should be aware of this potential complication, as early breastfeeding counseling and follow-up care with a qualified lactation professional can help these women reach their breastfeeding goals. Furthermore, identifying high-risk patients will ensure that any correctable causes of insufficient milk supply are corrected without adversely affecting infant nutrition [8].

2. Hormones Involved in Mammary Gland Development

Estrogen and progesterone stimulate breast development throughout puberty and pregnancy [17]. During puberty, a rise in circulating estrogen stimulates ductal growth. Early in pregnancy, progesterone and prolactin facilitate alveolar growth. Secretory differentiation or lactogenesis I occurs during midpregnancy and results in mammary epithelial cell differentiation. Later, the fall in progesterone after parturition results in secretory activation or lactogenesis II, stimulating milk secretion [8,17].

Women with PCOS have decreased levels of progesterone, which could potentially interfere with alveolar growth during pregnancy [8]. Furthermore, despite high circulating levels of estrogen in women with PCOS, hyperandrogenism may downregulate estrogen and prolactin receptors [8]. Insulin and glucocorticoids are also essential for lactogenesis to occur, but their signaling pathways and downstream targets are not completely understood [17].

3. Low Milk Supply and the Hyperinsulinemia-Androgen Connection

Androgens inhibit lactation [18] and are elevated in pregnant women with PCOS [19]. The first study to report an association between androgens and breastfeeding outcomes in women

Table 1: Main findings published in the literature concerning the relationship between PCOS and breastfeeding success

Study title	Year published	Reference #	Study design	Study description	Main results and conclusions
Pregnancy outcome in infertile patients with polycystic ovary syndrome who were treated with metformin	2006	[12]	Single-center retrospective case analysis	To analyze pregnancy health parameters and outcomes (including breastfeeding success) in patients with PCOS treated with metformin	Breastfeeding success was not affected by PCOS or metformin use Of the women that attempted breastfeeding, 78% (97/124) were successful and 22% failed Only four women attributed poor milk production as a reason for stopping breastfeeding
Breastfeeding in polycystic ovary syndrome	2008	[11]	Case-control study	To investigate the breastfeeding rate in new mothers with PCOS at 1-, 3-, and 6-month postpartum Androgen levels were analyzed and related to breastfeeding rate	Women with PCOS had a somewhat lower breastfeeding rate at 1-month postpartum in comparison to controls Breastfeeding rates were equal at 3- and 6-month postpartum DHEAS at gestational week 32 and 36 showed a weak negative association with breastfeeding in PCOS women
Breast size increment during pregnancy and breastfeeding in mothers with polycystic ovary syndrome: A follow-up study of a randomized controlled trial on metformin versus placebo	2012	[21]	Follow-up study of a randomized controlled trial (the PregMet study) Metformin versus Placebo	To study the significance of breast size increment in pregnancy and the impact of metformin during pregnancy on breastfeeding in women with PCOS	Neither metformin nor androgens had any impact on breast size increment in pregnancy or breastfeeding Women with PCOS that did not have breast size increment during pregnancy were more metabolically disturbed (obese, higher BP, serum triglycerides, and fasting insulin levels) and breastfeed less than those with breast size increment BMI correlated negatively with duration of partial breastfeeding
PCOS: Polycystic ovarian syndrome, DHEAS: Dehydroepiandrosterone sulfate, BMI: Body mass index, BP: Blood pressure					

with PCOS was a case-control study that included 36 women with PCOS and 99 controls [11]. The researches found that third-trimester dehydroepiandrosterone (DHEAS) levels were negatively correlated with breastfeeding rates at 1- and 3-month postpartum. However, in a later follow-up study of a randomized controlled trial (RCT) of metformin versus

placebo in women with PCOS (the PregMet study [20]), DHEAS, testosterone, and free testosterone index had no impact on breastfeeding [21].

Insulin resistance, followed by compensatory hyperinsulinemia, is frequently found in patients with

PCOS and is in part responsible for the increased levels of androgens in these women [22]. This so-called “hyperinsulinemia-androgen connection” is a vicious cycle, whereby insulin directly induces excess androgen production by theca cells [23] and decreases sex hormone-binding globulin (SHBG) production by the liver [24]. This leads to more free androgens, which in turn interferes with removal of insulin by the liver.

Approximately 30-40% of women with PCOS have impaired glucose tolerance, and 10% develop Type 2 diabetes mellitus by the age of 40 [6,16]. The previous studies have shown diabetes to be negatively associated with lactation [13]. One study found that mothers with gestational diabetes, especially mothers with insulin-dependent gestational diabetes, and obese mothers breastfed their children significantly less and for a shorter duration than healthy mothers [25]. Gestational diabetes has also been associated with delayed onset of lactogenesis [26]. In a case-control analysis, women diagnosed with low milk supply were significantly more likely to have had diabetes in pregnancy compared with women with latch or nipple problems. An independent effect of PCOS on the risk of low milk supply was not observed in a model that included diabetes, and the authors concluded that “PCOS as a risk factor for insufficient lactation may be limited to the subset of women with postpartum glucose intolerance” [13].

The association between low milk supply and insulin dysregulation was elegantly demonstrated in a recent study that compared gene expression in the milk fat globule transcriptome of women with or without low milk supply [27]. Milk fat globules are a rich source of mammary epithelial cell messenger RNA (mRNA), and using RNA-sequencing technology, the researchers found that protein tyrosine phosphatase, receptor type, F (PTPRF), which blocks the action of insulin to stimulate milk production, is overexpressed in the mammary gland of women with low milk supply. Therefore, PTPRF may serve as a biomarker linking insulin resistance with insufficient milk supply. Women with decreased insulin sensitivity might have a more sluggish increase in milk output in response to infant demand as a result of PTPRF overexpression in the mammary gland [27]. These findings

suggest that interventions targeting insulin action may be a promising and novel strategy toward improving milk supply in susceptible mothers [13].

Metformin could improve lactation through its favorable effect on insulin resistance. However, in a retrospective case analysis of pregnancy outcomes in 188 PCOS patients treated with metformin, breastfeeding success was not affected by PCOS or metformin use. Of the 124 women that attempted breastfeeding, 78% (97/124) were successful, and 22% (27/124) failed [12]. Only four women attributed poor milk production as a reason for stopping breastfeeding. Furthermore, in a follow-up study of an RCT of metformin versus placebo in pregnant women with PCOS (the PregMet study [20]), metformin had no impact on breastfeeding [21].

Recently, a small-scale phase I/II RCT of metformin versus placebo has been conducted, with results pending, to test whether metformin is safe and potentially effective in treating low milk supply in insulin resistant and pre-diabetic mothers [28]. Primary outcome measures will include milk output (at baseline and weeks 2 and 4 post-intervention), and secondary outcome measures will include safety, mammary gene expression (using mammary epithelial cell mRNA and RNA-sequencing), sensitivity and specificity of maternal fasting plasma glucose (FPG) in predicting low milk supply, and change in milk output among completers. The results of this study will inform a future larger double-masked RCT of adjuvant metformin treatment versus placebo for early postpartum low milk supply in women with insulin resistance based on the presence of at least one of the followings: Elevated FPG (defined as >95 g/dL), history of PCOS or gestational diabetes, or current abdominal obesity. Thus, results of this pilot study are eagerly awaited and will have a major impact on treatment strategies for women with gestational diabetes, pre-diabetes, or PCOS that present with low milk supply.

4. Metabolic Disturbances, Obesity, and Breastfeeding

Animal models have demonstrated that obesity is associated with marked abnormalities in mammary alveolar development [29]. Mammary adipose tissue

may produce locally effective concentrations of estrogen that could alter mammary gland development and lactation [17].

Approximately one-half of women with PCOS are obese [30], and women with pre-gravid obesity, irrespective of the presence of PCOS are less likely to initiate and sustain breastfeeding [31,32]. Maternal obesity is also associated with delayed onset of lactogenesis [33] and a lower prolactin response to suckling [34]. Therefore, women with PCOS may be at an increased risk for insufficient milk supply due to their underlying obesity.

In the first case-control study of breastfeeding in women with PCOS, Vanky et al. reported reduced breastfeeding rates in the early postpartum period in women with PCOS; however, the controls were not matched for body mass index (BMI). In the follow-up study of an RCT of metformin versus placebo in pregnant women with PCOS (the PregMet study [20]), the significance of breast growth in pregnancy, indexed by a change in bra size, on breastfeeding outcomes was assessed [21]. The duration of both exclusive and partial breastfeeding correlated positively with breast size increment and the increase in breast size was unrelated to maternal BMI or change in BMI. Indeed, increased BMI was related to a shorter duration of partial breastfeeding. Furthermore, those with no breast growth were more metabolically disturbed (obese had higher blood pressure, serum triglycerides, and fasting insulin levels). The authors suggested a new way of interpreting past epidemiological studies that have shown breast milk to protect offspring from obesity and diabetes [14,35,36]. Namely, because mothers with decreased breastfeeding rates were more obese and had higher insulin levels, their offspring may be more prone to develop obesity, independent of breast milk. Simply put, women who are not able to breastfeed are metabolically inferior compared with those who breastfeed easily [21].

Similarly, studies examining the long-term benefits of breastfeeding on maternal metabolic risk factors have yielded mixed results, and very few studies provide direct evidence for lactation's lasting effects on the development of cardiometabolic diseases [37]. Although lactating compared with non-lactating women have better metabolic parameters, including lower lipid levels [38], lower fasting

and postprandial blood glucose [39,40], and greater insulin sensitivity [39], few studies have measured these biochemical parameters longitudinally [37]. Moreover, as previously mentioned, it is difficult to ascertain whether non-lactating women are at the start "metabolically inferior" compared to lactating women [21]. Therefore, while breastfeeding may prevent the development of the metabolic syndrome, pre-existing metabolic dysregulation may hinder attempts at breastfeeding [41]. Women with PCOS are at an increased risk of developing the metabolic syndrome [42], and these characteristics may make them more susceptible to lactation difficulties. One study examined the effect of lactation on insulin resistance, glucose and insulin metabolism, and biological markers of insulin resistance (SHBG and insulin-like growth factor binding protein-1 [IGFBP]) in fully breastfeeding women with PCOS and normal lactating women during the postpartum period as well as after weaning [43]. 12 lactating women with PCOS and six normal lactating women were matched for BMI, and during the study, BMI remained unchanged was comparable between the groups. Lactation had no significant effect on peripheral insulin resistance (measured by the insulin tolerance test) in women with PCOS, but fasting insulin concentrations were lower after weaning in the lactating PCOS group than in the same patients before pregnancy. Therefore, although lactation may improve metabolic control in these patients shortly after weaning, the long-term benefits remain uncertain and should be investigated in future prospective studies.

5. Conclusion

Studies, albeit scarce, have reported conflicting results when examining breastfeeding success in women with PCOS [11,12], and the divergence of the PCOS phenotype may be responsible for the heterogeneous results to date. Specifically, insulin resistance as a feature of PCOS may have a contributing or even essential role in the development of lactation dysfunction and may be the missing link. Considering the high prevalence of PCOS among women of childbearing age and the known benefits of breastfeeding for both mother and child, it is evident that more research in this area is needed. Future research should focus on the underlying mechanisms

of PCOS-related low milk supply and further examine the role of insulin resistance. This knowledge will help design and implement interventions that will enable more women with PCOS to meet their infant feeding goals. Furthermore, understanding how insulin resistance and PCOS affect lactation will broaden our understanding of diabetes as a whole, potentially leading to new therapeutic strategies for treating Type 2 diabetes.

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