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CASE REPORT

Labetalol-Associated Raynaud's Phenomenon of the Nipple: A Rare Case Report with Review of Literature

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Keywords Gestational hypertension · Raynaud's phenomenon · Nipple pain · Labetalol · Nifedipine

Abbreviations

GHT	Gestational hypertension
RP	Raynaud's phenomenon
RPN	Raynaud's phenomenon of the nipple
UK	United Kingdom

Introduction

Raynaud's phenomenon of the nipple (RPN) is one of the several etiologic factors that result in nipple pain [1]. It is an extremely painful condition and primarily affects pregnant and lactating women, resulting in cessation of breastfeeding [1, 2]. It is usually idiopathic, but has been scarcely reported to be associated with Labetalol use [2–4].

In addition to Labetalol-associated RPN, earlier case reports from United Kingdom (UK) reported that women had history of cold-associated RPN [2, 4]. Thus, these cases already had predisposing conditions that were worsened by Labetalol. However, in India, especially central part of India, tropical climate predominates and there is an absence of environmental factors triggering the RPN. Herein, we report a case of labetalol-associated RPN, the first from India, in a 34-weeks pregnant woman.

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Case Description

A 30-year-old Indian woman, gravida 1, para 0, with no significant medical history was diagnosed with gestational hypertension (GHT) during her regular antenatal check-up at 34-weeks of gestation. She was a booked case at a private hospital with regular multiple antenatal visits. During this visit, she had a blood pressure of 140/92 mmHg on 3 occasions, trace albuminuria, normal blood sugar, and normal deep tendon reflexes. Though mild edema feet was present, there was absence of preeclampsia warning signs including headache, blurring of vision, right upper quadrant pain, nausea, or vomiting. On routine investigations, patient had mild anemia (10.2 gm%), while other blood counts, and liver and renal functions were with normal limits.

For GHT, she was initiated on tablet Labetalol 100 mg twice daily (morning 8am and night 8pm). However, around 1-h after the first dose, she complained of severe burning sensation with severe tenderness at nipple-areola area. She felt as if her breast was just about to burst, though there was no breast engorgement or color change. This sensation lasted for 2–3 h, then subsided on its own. On following morning, within 45 min of intake of second dose of tablet Labetalol, she experienced similar symptoms, for which she immediately contacted her obstetrician.

On examination, general condition was normal. Local breast examination did not reveal any engorgement or change in color. On further enquiry, she did not reveal any history of similar complaints involving nipple or extremities. The blood pressure was found to be raised (146/98 mmHg), for which opinion of general physician was obtained. Tablet Labetalol was withdrawn and tablet Nifedipine 20 mg twice daily was initiated, following which she did not experience any adverse events and pregnancy remained uneventfully till 37-weeks of gestation. Subsequently, in view of GHT and fetal distress, she underwent uneventful caesarean section, and delivered a healthy female child weighing 2.7 kg.

Discussion

Initially, in 1862, Maurice Raynaud described the Raynaud's phenomenon (RP) as an episodic vasospastic ischemia of the digits [2]. It is usually experienced as a response to an emotional or environmental stress and can be either primary (idiopathic) or secondary (cancer, autoimmune diseases, lifestyle conditions such as smoking, and certain medications) [1]. It affects 3–5% of the general population, and is four times more prevalent among women than men [5]. Moreover, it affects around 22% women in the childbearing age group. It frequently involves extremities, however other areas including coronaries, tongue, gastrointestinal tract, placenta, nipple, and penis are reported to be involved [1, 5].

In 1970, Gunther first documented nipple vasospasm. However, it was Coates, in 1992, who described and associated the nipple vasospasm to RP [4]. Pregnant and lactating women are at an increased risk of developing RPN due to excessive vasomotor response that is ascribed to higher levels of estrogen and stress. The former acts by increasing the expression of smooth muscle α2C-adrenoreceptors, thereby triggering cold-associated constriction of cutaneous vessels. While, the latter leads to greater release of norepinephrine that, in turn, acts on upregulated endothelial adrenergic receptors [1]. Available literature mostly describes RPN in association with lactation and this relationship can be ascribed to lactation-induced physiologic and emotional stressors which lead to vasomotor responses.

Drug-associated RP of extremities is well described in the literature and reported as an adverse event to several class of drugs including chemotherapies (bleomycin and cisplatin), tyrosine kinase inhibitors, β-adrenoceptor blockers, and ergot alkaloids [2, 4]. Moreover, RP of extremities is a known Labetalol-associated adverse event [4]. Initial reports from Western part of the world have described Labetalol-associated RPN in pregnant women [2–4]. However, to best of our knowledge, Labetalol-associated RPN has not been reported from India.

In 2012, the first documented Labetalol-associated RPN was reported from UK, involving a 37-year-old pregnant woman [2]. Subsequently, between 2012 and 2013, similar cases, involving 3 pregnant women, aged 21 to 40 years, were reported to Netherlands Pharmacovigilance Centre. In addition to 3 cases from Netherlands and 1 case from UK, Eudravigilance reports additional 2 cases, 1 each from Denmark and UK. Moreover, database of World Health Organization reports another 2 cases [3]. Recently, in 2019, Labetalol-associated RPN was reported in 30-year-old white pregnant woman from UK [4]. Thus, till date, a total of 9 Labetalol-associated RPN cases have been documented. However, of these 9 cases, pregnancy status could be confirmed in only 5.

Given the fact that GHT can rapidly progress to pre-eclampsia and eclampsia, it should be closely monitored and treated. Moreover, due to its excellent safety profile, Labetalol is approved for the treatment of pregnancy induced hypertension. In third trimester of pregnancy, Labetalol or Methyldopa are used as the first-line drugs for the management of GHT [3]. Labetalol has a selective α1 and non-selective β receptor blocking activity, thus unlike pure β receptor blockers, its dual action results in less risk of reduction in uteroplacental blood flow [4]. However, the current summary of product characteristics does not include RPN as a Labetalol-associated adverse event. Thus, the precise mechanism by which Labetalol induces RP remains to be elucidated.

Apart from RPN, a variety of conditions are reported to be associated with nipple pain, including problems with infant latch-on and positioning, plugged lactiferous ducts, milk letdown pain, psoriasis, dermatitis, and secondary infections such as *Candida albicans* [3]. Some patients with RPN have history of nipple trauma, RP of extremities, or personal or family history of thyroid disorder. Moreover, it can be triggered in condition such as lactation, swimming in cold water, entering an air-conditioned room, or opening the refrigerator door [5]. Though there is absence of officially recommended diagnostic criteria for RPN, we could find a criteria described by Barrett et al. They diagnosed RPN in patients with chronic deep breast pain (usually, lasting 4 or more weeks) that subsided with targeted therapy for RP and patients had a minimum of two of the following features, including observed or self-reported change in color of the nipple, particularly when exposed to cold (white, blue, or red); sensitivity to cold or cold exposure leading to change in color of the hands or feet; or absence of response to oral antifungal agents [1]. In our patient, there was absence of any of the above-mentioned triggering factors. She had normal antenatal check-up until 34-weeks of gestation. She received usual iron, folic acid, and calcium supplements and there was no prior exposure to Labetalol.

If GHT remains uncontrolled or adverse events are intolerable, alternative antihypertensives including Nifedipine, Methyldopa, and Hydralazine should be considered. Nifedipine, a calcium-channel blocker, decreases entry of calcium into cells by blocking calcium channels, thus reduces contraction of smooth muscles and cause vasodilation, thereby decreasing blood pressure. Currently, Nifedipine is the first-line drug for treatment of RP [5], and has been reported to resolve RPN in various cases [4, 5]. Likewise, in our case, initiation of Nifedipine did not result in recurrence of symptoms and pregnancy remained uneventful with excellent control of blood pressure.

Labetalol attains it peak effect within 1–2 h of administration [3]. In our patient, onset of symptoms was within 45–60 min of intake and lasted for 2–3 h. In other cases,

onset of symptoms is reported to be within 30–60 min of intake, lasting for 20–30 min [3, 4]. Moreover, in all the cases, including ours, symptoms resolved spontaneously. Thus, onset and duration of symptoms coincides with the known pharmacokinetics of Labetalol. Though, Labetalol-associated RPN is reported as a non-serious adverse event [3], it produces great amount of anxiety and discomfort in already stressful pregnant condition. Due to embarrassment, the patient does not report RPN and it usually goes unnoticed [2]. Thus, obstetricians should be made aware of Labetalol-associated RPN and counsel the patients regarding its occurrence. Patients should be encouraged to report any nipple discomfort associated with Labetalol use.

Conclusion

Labetalol is a commonly used first-line drug for the treatment of GHT. In this report, we present a rarely documented adverse event associated with Labetalol use in pregnancy. We observed a causal relationship between Labetalol and RPN. When prescribing Labetalol in pregnancy, patient should be made aware of nipple-related discomfort and encouraged to report it on an urgent basis. Moreover, Labetalol should be replaced with alternative antihypertensive drugs.

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Declarations

Conflict of interest No financial support and no potential conflict of interest relevant to this article was reported.

Consent to publish Consent to write and report this case was obtained from the patients.

Ethical statement Approval of the Institutional Ethics Committee was not required.

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