Case Report

The Effects of Nitric Oxide Production and Lymphedema Treatment on A Pregnant Female with A History of Recurrent Abortion: A Case Report

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ABSTRACT

Background: The association between lymphedema and recurrent abortion is not fully clarified. In the present case, I report the occurrence of acute dermatolymphangio-adenitis [previously: cellulitis] about three days before each abortion and the effect of non-surgical treatment of lymphedema on pregnancy.

Case presentation: A 30-years old nulliparous pregnant female complains of right lower limb lymphedema with a history of recurrent abortion. Measurement of Lymphedema circumference and serum nitric oxide assay were done before, during, and after treatment. She was treated by intermittent pneumatic compression to produce wall shear stress on blood and lymphatic vessels, chemical compression by a zinc oxide paste bandage, and, a special elastic stocking. There was a statistically significant increase in serum nitric oxide concentration [F-test=75.814, p<0.001] together with a statistically significant decrease in lymphedema circumference [F-test=24.564, p=0.005]. After treatment there were no acute dermatolymphangioadenitis attacks, the lymphedema subsided and she delivered a full-term healthy infant.

Conclusions: This study aimed to report the safety and efficacy of conservative treatment of lymphedema in a pregnant female with a history of recurrent abortion.

Keywords: Lymphedema; Abortion; Nitric Oxide; Pregnancy; cellulitis

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INTRODUCTION

Lymphedema is a chronic disfiguring disease characterized by tissue swelling due to the accumulation of protein-rich fluid that’s usually drained through the body's lymphatic system. It affects up to 250 million people worldwide \[^1\].

Lymphedema may be primary or secondary. Secondary lymphedema is more common and developed secondary to either direct or indirect injury to the lymphatic system. The most common cause of secondary lymphedema worldwide is lymphatic filariasis \[^2\].

Recurrent attacks of Acute dermatolymphangioadenitis [ADLA previously “cellulitis”] complicate the clinical course of lymphedema. The affected limb becomes swollen, red, hot, and tender with inflammation of the draining lymph nodes due to secondary bacterial infection \[^3\].

Multi-drug-resistant methicillin-resistant Staphylococcus aureus [MRSA], cephalosporin-resistant Escherichia coli and carbapenem-resistant Pseudomonas aeruginosa were isolated from Lymphatic Filariasis patients \[^4\].

Recurrent abortion is defined as two or more abortions before the 20th gestational week of gestation. Many risk factors are associated with recurrent abortion e.g., endocrine disorders, immunologic, metabolic, genetic, male-related factors, and infectious diseases \[^5\].

There is a significant association between healthcare-associated infection of women and miscarriage. The main causative agents of healthcare-associated infection of women are Escherichia coli, Enterobacter spp., Klebsiella pneumoniae, Enterococcus faecalis, Staphylococcus aureus and Pseudomonas aeruginosa \[^6\].

Multiple mechanisms can be used by pathogens to cross the placental barrier. The presence of pathogenic organisms in the placenta induces a maternal immune response to infection that could result in miscarriage \[^7\].

Intermittent pneumatic compression devices assist in lymphedema management by decreasing limb volume \[^8\]. Both intermittent pneumatic compression and compression stockings induce haemodynamic transient shear stress on blood vessels which promote endothelial cells to release nitric oxide \[^9\]. The ultralow molecular weight of nitric oxide enables it to freely diffuse into biological membranes to exert its antibacterial action \[^10\].

This study aimed to report the effects of conservative treatment of lymphedema in a pregnant female with a history of recurrent abortion.

Case presentation

A 30-years old nulliparous female patient presented with right lower limb lymphedema. It is a filarial lymphedema due to the earlier detection of Wuchereria bancroftii microfilaria. She had a history of recurrent abortions. Three consecutive abortions occurred two years after the lymphedema developed at 12,16 and 9 weeks of pregnancy. To specify the cause of the abortion, a blood hormonal profile, TORCH screen, and chromosomal study were done. The laboratory investigations revealed no obvious cause. An interesting finding in the present case is the occurrence of acute dermatolymphangioadenitis in the lymphematous limb about three days before each abortion.

The patient’s physical examination revealed right lower limb lymphedema with early manifestation of acute dermatolymphangioadenitis. The laboratory investigations revealed a leukocytosis [WBC count was 15,000/ml], a negative blood film for microfilaria, and negative filarial antigenemia. Human chorionic gonadotropin was assayed, and fortunately, she was pregnant [three weeks gestational age]. Serum Nitric oxide was assayed [ELISA, Elabscience, USA] before treatment and at the end of every week during the first month of pregnancy [during treatment] and then every month till delivery [after treatment]. The mean [average] lymphedema circumference [Fig. 1] was estimated at different levels at the same time as in the nitric oxide assay \[^11\].

She was treated by intermittent pneumatic compression three sessions per week for four weeks by using the lymphedema compression device [Care-med Ltd] according to the manufacturer's instructions. The pneumatic compression device consists of a pump that applies pressure [80–100 mmHg] to multiple individual chambers inside the garment. The chambers inflate in sequence from distal to proximal, hold briefly, and then deflate for a brief intermission before resuming the distal-to-proximal cycle. The duration of the session was
30 minutes followed by chemical compression by a zinc oxide-impregnated paste bandage applied over the lymphedematous limb then wrapped by a cotton layer and bandage and wearing a special elastic stocking till the next session.

RESULTS

After four weeks of treatment, the mean [average] lymphedema circumference decreased, without acute dermatolymphangioadenitis attacks. The serum level of nitric oxide concentration was increased during and after treatment within the range of physiological level [Fig. 2 and table 1]. The reference value for serum nitric oxide concentration is 11.5 to 76.4 μmol/L in women. The increase in serum nitric oxide level was statistically significant [F-test=75.814, p<0.001]. Wearing the special elastic stocking which is formed of an inner cotton layer and outer tuff elastic layer extended during and after pregnancy to prevent the recurrence of lymphedema. The decrease in lymphedema circumference was statistically significant [F-test=24.564, p=0.005]. She delivered a healthy full-term infant.

Table [1]: Relation between serum nitric oxide concentration and the main lymphedema circumference before, during and after treatment

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>During treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1st month</td>
<td>2nd M</td>
</tr>
<tr>
<td>Serum nitric oxide concentration [μmol/L] *</td>
<td>12.1</td>
<td>34.5</td>
<td>43.7</td>
</tr>
<tr>
<td>F-test</td>
<td>=75.814, p&lt;0.001</td>
<td></td>
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<tr>
<td>The mean [average] Lymphedema circumference [cm]</td>
<td>85</td>
<td>62</td>
<td>54</td>
</tr>
<tr>
<td>F-test</td>
<td>=24.564, p=0.005</td>
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*Micromole per liter [μmol/L] / week [w] / month [m].
DISCUSSION

The risk of abortion and/or postnatal deaths is higher in lymphatic filariasis-infected females, especially in endemic areas. Lymphatic filariasis is the probable cause of the failure of two cycles of in vitro fertilization (IVF) with good-quality embryos. In an extended study for identifying the lymphatic filariasis morbidity in Ghana, the authors reported that lymphedema may cause infertility and miscarriages. The lymphedema progress either during or after the acute dermatolymphangioadenitis attacks.

Pneumatic compression therapy (PCT) is one of the guidelines for lymphedema management. PCT decrease the infection rate and hospital admissions of lymphedema patients. Pneumatic compression delivers the retained fluid to functional lymphatics and decreases the lymphatic load, increase lymphatic reabsorption, and improves trophic changes of skin elasticity. It improves clinical symptoms such as heaviness, itching, pain, and quality of life.

Lymphoscintigraphy has shown lymph movement in response to pneumatic compression with 50 – 125 mmHg. The assessment of lymph flow during intermittent pneumatic compression has demonstrated that the optimal pressure for optimal flow was 80 mmHg. The pneumatic compression increases intravascular flow, shear, and compressive strain on the vascular endothelium with the resulting release of nitric oxide.

Shear stress is produced by the mechanical frictional force of blood flow and contraction of the heart. It is a well-known mechanical signal that affects endothelial cells [function, morphology, and gene expression]. Endothelial nitric oxide synthase (eNOS) derived from the endothelium is constitutively expressed and produces nitric oxide in response to shear stress. Shear stress is produced by the compression of the legs using pneumatic cuffs.

Shear stress activates endothelial nitric oxide synthase through phosphorylation, thus producing endothelial nitric oxide, which is important for increasing blood flow and an important signaling molecule that improves microvascular dysfunction and down-regulates the inflammatory cascade. The low concentrations of nitric oxide produced by eNOS in the vessel wall mediate anti-inflammatory, antithrombotic, and vasodilation effects.

Nitric oxide is an endogenously produced gaseous molecule involved in multiple physiological processes. In the body, nitric oxide is produced enzymatically from L-arginine by one of three nitric oxide synthase (NOS) isoforms: endothelial (eNOS), neuronal (nNOS), and inducible (iNOS). NO has antibacterial and anti-biofilm activity through its physicochemical properties. Nitric oxide is a broad-spectrum antibacterial agent including both Gram-positive bacteria.
and Gram-negative organisms, making it an attractive alternative to traditional antibiotics for treating infections [23].

Nitric oxide has an important defense against several pathogens by cytotoxic mechanism. Nitric oxide can react with superoxide that is endogenously derived from the respiration process of bacteria to generate reactive oxygen/nitrogen species, including the powerful oxidant NO radical [NO•], peroxynitrite [ONOO−], and dinitrogen trioxide [N2O3], which exhibit antibacterial effects on various bacteria by causing the oxidative or nitrosative stress such as DNA deamination and lipid peroxidation [18].

Howlin et al. demonstrated that submicromolar nitric oxide concentrations effectively treated Pseudomonas aeruginosa [P. aeruginosainfection in cystic fibrosis [24]. Numerous studies have reported that nitric oxide displays potent antibacterial effects in vitro and in skin infection models when used at proper concentrations. Nitric oxide produced endogenously by endothelial cells stimulates cell proliferation, cell migration, and differentiation of stem cells leading to enhanced vascularization, collagen synthesis, rapid wound healing and skin regeneration [25].

Nitric oxide-based antimicrobials have become popular due to their significant role in the immune system and researchers’ need for new antibiotics since typical antibiotics develop resistance within 2 years [26].

Compression elastic stockings have been identified to raise the wall shear stress [WSS] in the superficial veins and lymphatic vessels of the leg in humans. Wearing knee-high compression stockings significantly raises the leg pump lymph pressure and promotes nitric oxide [NO] production by endothelial nitric oxide synthase [27].

Chemical compression by wrapping the limb with zinc oxide alleviates skin inflammation and promotes wound healing. It is economical and efficient in reducing the incidence of skin infection [28, 29].

Conclusion: This study presented the safety and efficacy of conservative treatment of lymphedema and acute dermatolympangio-adenitis in a pregnant female with a history of recurrent abortion. There is a significant increase in serum nitric oxide together with a significant decrease in lymphedema circumference after conservative treatment.

Conflict of Interest and Financial Disclosure: None.

REFERENCES


