



Araştırma Makalesi /Research Article

Erken Laktasyon Döneminde Uygulanan Refleksolojinin Vasküler Endotelial Büyüme Faktörü (VEGF), Endostatin, Matris Metalloproteinazlar (MMP) ve Trombospondin (TSP) Düzeyleri Üzerindeki Etkisi

The Effect of Reflexology Applied in the Early Lactation Period on Vascular Endothelial Growth Factor (VEGF), Endostatin, Matrix Metalloproteinases (MMP) and Thrombospondin (TSP) Levels

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Öz

Amaç: Refleksoloji, kadın hayatının önemli dönemlerinden biri olan laktasyon sürecini olumlu yönde etkileyen en yaygın tamamlayıcı tıp yöntemlerinden biridir. Bu çalışmanın amacı, doğum sonrası dönemde refleksolojinin anjiyojenik ve anti-anjiyojenik belirteçler olan vasküler endotelial büyüme faktörü (VEGF), matris metalloproteinazlar (MMP), endostatin ve trombospondin (TSP) seviyeleri üzerindeki etkisini belirlemektir.

Gereç ve Yöntem: Araştırma deneysel olarak planlanmış ve veriler Mart-Ağustos 2015 tarihleri arasında Hafsa Sultan Hastanesi Kadın Hastalıkları ve Doğum Anabilim Dalı'nda toplanmıştır. Çalışma, 60'ı deney ve 30'u kontrol grubu olmak üzere 90 kadından oluşmuştur. Deney grubundaki 30 kadının ayaklarında endokrin sistem ve üreme organları bölgesine ve diğer 30 kadının ayaklarında lumbosakral bölgeye refleksoloji uygulanmıştır. Kontrol grubundaki kadınlar rutin sağlık bakımı almıştır. VEGF, MMP, endostatin ve TSP seviyeleri enzim bağlantılı immüno sorbent analiz (ELISA) yöntemi ile ölçülmüştür. Elde edilen verilerin değerlendirilmesinde statistical package for the social sciences (SPSS) 15.0 istatistik programı kullanılmıştır.

Bulgular: Refleksoloji grubunda VEGF seviyesinde bir artış görülürken, MMP ve Endostatin seviyelerinde istatistiksel olarak anlamlı bir azalma olmuş ve TSP'de ise anlamlı bir değişiklik gözlenmemiştir. Lumbosakral bölge endokrin/üreme sistemi ile karşılaştırıldığında TSP seviyesinde istatistiksel olarak anlamlı bir azalma vardır.

Sonuç: Lumbosakral ve üreme organlarına uygulanan refleksolojinin; laktasyon sırasında anne sütü üretimi açısından anjiyojenik bir belirteç olan VEGF ve anti-anjiyojenik belirteçler olan MMP ve Endostatin üzerinde etkisi olmuştur.

Anahtar Kelimeler: Endostatin, Laktasyon, MMP, refleksoloji, Trombospondin, VEGF

Abstract

Objective: Reflexology is one of the most widely used methods of complementary medicine which positively affects the lactation process, which is one of the important periods of female life. The aim of this study was to determine the effect of reflexology on vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMP), endostatin and Thrombospondin (TSP) levels, which are angiogenic and antiangiogenic markers in postpartum period.




Methods: The research was planned experimentally and the data were collected between March and August 2015 at Gynecology and Obstetrics Department of Hafsa Sultan Hospital. The study consisted of 90 female; 60 experimental and 30 control groups. Reflexology was performed on the endocrine system and reproductive organs region in 30 women's foot and on the lumbosacral region in the other 30 women's foot in the experimental group. Control group received only routine health care. VEGF, MMP, endostatin and TSP levels were measured by using enzyme-linked immuno sorbent assay (ELISA) method. Statistical package for the social sciences (SPSS) 15.0 statistical program was used to evaluate the data obtained.



Results: While there was an increase in VEGF level in the reflexology group, there was a statistically significant decrease in MMP and endostatin levels, and no significant change in TSP was observed. When the lumbosacral region is compared according to the endocrine / reproductive system, there is a statistically significant decrease in TSP level.

Conclusion: Reflexology applied to the lumbosacral and reproductive organs; It had an effect on VEGF, which is an angiogenic marker, and MMP and endostatin, which are antiangiogenic markers, in terms of breast milk production during lactation.

Keywords: Endostatin, Lactation, MMP, reflexology, Thrombospondin, VEGF

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INTRODUCTION

Women go through many physiological stages throughout their lives. In the fertile period, one of the most important life stage of women is the lactation period. The lactation process in the postpartum period is very important for breast milk production. It is a well-known fact that breast milk has properties that fully support the development of the baby and is a unique nutrient for babies. Breastfeeding has been the healthiest method of reaching babies with breast milk, which is a unique food in newborn nutrition in almost all eras and cultures¹. Lactation is a substantially complex process that includes not only breast tissue and endocrine system but also psychological, genetic and environmental factors². Reflexology can be a good method during this period.

Reflexology is one of the most used methods of complementary medicine, and it is the activation of the self-healing power of the body by dissolving the energy blocked in specific parts of the body with special scrubbing movements applied to the ears, hands and feet³. It is thought that especially, each part of the body corresponds to a specific point on the feet and the pressure applied to these points can relax and balance the whole body. These points are connected with energy channels, regions and / or meridians, internal organs and structures. In case of illness or imbalance, these energy channels in the body are blocked⁴. This process is called "detoxification" since this pressure on reflex areas is effective in the absorption and reduction of calcium, lactate and uric acid crystals⁵. The pressure applied to these reflex points with special hand and finger techniques leads to physiological changes in the body by reducing stress⁶. With this method, the self-healing mechanism of the body is activated and a physiological relaxation is provided in the body. In addition, it helps to improve the blood flow of the body, maintain homeostasis and reduce tension⁵. Growth factors are proteins ranging in weight from 4000 to 60,000 daltons, even small amounts of which can affect cellular activities. These factors affect cells through endocrine, paracrine, autocrine or intracrine mechanisms. If a cell carries both a growth factor and its receptor, it has a growth ring that stimulates it⁷.

Vascular endothelial growth factor (VEGF) is one of these growth factors. They function in angiogenesis and lymphangiogenesis. VEGF is the most important and the most emphasized one

among angiogenic molecules and it is also known as vascular permeability factor (VPF)⁸. VEGF is an endothelial cell-specific mitogen that causes strong angiogenesis and vascular permeability⁹. Matrix metalloproteinases (MMPs) are zinc (Zn) and calcium (Ca) dependent neutral endopeptidases family, which contain more than 23 endoproteinases, which are Zn dependent and capable of degrading the entire matrix. They are synthesized by many cell groups, mainly macrophages and lymphocytes. They cause blood-brain barrier (BBB) destruction, leukocyte infiltration, demyelination, axonal damage and astrogliosis¹⁰.

Angiogenesis has endogenous inhibitors in the body. Endostatin, a 20-kDa molecular weight component derived from the carboxy terminus of collagen type XVIII, was firstly developed by O'Reilly et al. isolated from mouse hemangioma endothelioma cells. It prevents the proliferation and migration of endothelial cells¹¹.

Thrombospondins (TSP) are calcium-binding glycoproteins that occur naturally in the extracellular matrix. They are adhesive proteins that provide cell-cell and cell-matrix interactions, and 5 subtypes have been defined¹². TSP-1 has a role in suppressing endothelial cell proliferation, cell movement and metastasis in cancer cells¹³.

Lactation is a process that begins during pregnancy, and the development of breast tissue also accompanies this process. It is known that angiogenic factors play a role in the development of breast tissue. Since reflexology is a supportive treatment that positively affects breastfeeding, the aim of this study is to determine the effect of reflexology applied to women giving birth on angiogenic factors.

MATERIALS AND METHODS

The research was conducted in Manisa Celal Bayar University (MCBU) Hafsa Sultan Hospital Gynecology and Obstetrics Service, Health Services Vocational School and Midwifery Department. According to the analysis conducted using the G-Power 3.1.9.7. program, the sample size was taken as $\alpha=0.05$, power $(1-\beta)=0.80$, intervention and control group ratio was 1:1:1, and the effect size was 0.5603173 for all three groups¹⁴. The smallest sample size was calculated as a total of 87 women in the postpartum period, including 29 women for each group. Considering the possibility of data loss during the study, it was planned to conduct the study with 90 women in postpartum period. Participants who met the

inclusion criteria were randomly selected to the study or control group by simple randomisation. The research data was consist of total of 90 female in the postpartum period, including 60 in the experimental group and 30 in the control group, who met the inclusion criteria and volunteer to participate to the research and gave normal birth in the Gynecology and Obstetrics Service of MCBU Hafsa Sultan Hospital. Reflexology was studied on the endocrine system and reproductive organs in feet in 30 women and on the lumbosacral region in feet in the other 30 women in the experimental group.

Having a vaginal birth, being in the 18-35 age group, starting breastfeeding in the first hour and within the first 3-4 hours after birth, breastfeeding at least 2 times in a 4-hour period, having no breast problems that would prevent breastfeeding, being fed, mobilized, and emptying the bladder, Women who did not have any chronic disease, were not diagnosed with any psychological disease, had a body mass index (BMI) ≤ 30 and agreed to participate in the study were included in the study. Reflexology was applied to the experimental group included in the study. Foot reflexology was preferred in the study because the area was wider than other reflexology areas and pressure could be applied to each reflex point more easily. The practice started with the right foot and then moved on to the left foot. The feet were evaluated for scars, wounds and edema. Pressure was applied to the reflex points with knurling, push-pull, squeezing and stroking movements.

If there are no complications in postpartum women admitted to the maternity service, hemogram control is routinely performed after four hours. During this control, 1 cc of blood was drawn in this study. All collected blood was stored at -80 degrees after being separated into serum. Then, all blood was studied at the same standards using the same analysis method. VEGF, MMP, endostatin and thrombospondin levels were measured using the enzyme-linked immuno sorbent assay (ELISA) method.

This study was conducted in accordance with the 1975 Declaration of Helsinki. This study was approved by the Local Ethics Committee of MCBU Faculty of Medicine with the decision dated 05.03.2015 and numbered 85.252.386-04 and the "Approval Form for Storage of Biological Material for Education and Research Purposes" was approved by the same ethics committee decision.

Moreover, informed consent was obtained from each patient.

Statistical Analysis

The data obtained from the research were analyzed using the Statistical Package for Social Sciences (SPSS) for Windows, version 15.0. The value of $p < 0,05$ was accepted statistically significant in comparisons. Mean \pm standard deviation (SD), number percentage distribution, Mann-Whitney U and Kruskal Wallis test analyses were performed to evaluate the data collected in accordance with the purpose of the study.

RESULTS

In this study, it was aimed to investigate the effect of reflexology on VEGF, MMP, endostatin and thrombospondin levels, which are angiogenic and antiangiogenic markers, in women who were applied reflexology on the pituitary and reproductive organs and lumbosacral area on feet by using the ELISA test in the postpartum period. This study conducted with the experimental (Endocrine/Reproductive System, Lumbosacral Region) and control groups, no statistically significant difference was found between the groups in terms of age, education and income (Table 1).

Table 1: Examination of the socio-demographic characteristics of women in the experimental group (Group 1), in whom reflexology was performed on the pituitary and reproductive organs, and in the experimental group (Group 2), in which reflexology was performed on the lumbosacral area, and in the control group.

Sociodemographic Characteristics	Control Group		Experimental Group				χ^2	p
	Group		Group 1		Group 2			
	n	%	n	%	n	%		
Age Groups								
26 years and under	12	40	18	57.3	10	34.4	4.024	0.134
27 years and above	18	60	12	42.7	20	65.6		
The average age	27.11 \pm 4.41		26.05 \pm 4.59		27.62 \pm 4.30		2.266	0.322
Educational Status								
Literate/Primary School Graduate	10	34.3	16	51.4	6	22.9	12.931	0.228
Secondary School Graduate and Above	20	65.7	14	48.5	24	77.1		
Income status								
Income less than expenses	2	5.7	6	22.9	3	11.4	5.705	0.222
Income equal to expenses	23	74.3	21	68.6	22	71.4		
Income more than expenditure	5	20.0	3	8.6	5	17.1		

χ^2 : K Independent Samples-Kruskal Wallis

Endostatin and MMP decreased ($p < 0.05$), and TSP level increased statistically ($p < 0.05$) when the control group and endocrine/reproductive system were compared. MMP level decreased statistically ($p < 0.05$) when the control group and the lumbosacral region were compared, while VEGF, endostatin and TSP levels were not statistically significant. MMP level increased statistically ($p < 0.05$) when the lumbosacral region was compared with the endocrine/reproductive system, while TSP level decreased statistically ($p < 0.05$) (Table 2, Figure 1).

Table 2: VEGF, MMP, Endostatin and TSP levels in experimental and control groups

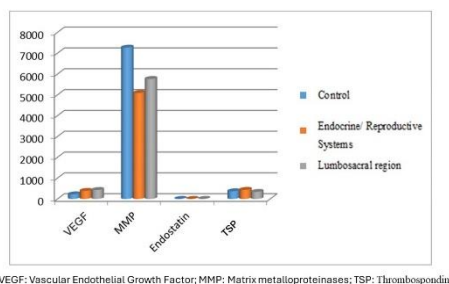
	VEGF (ng/L) Mean±SD	MMP (ng/L) Mean±SD	Endostatin (ng/L) Mean±SD	TSP (ng/L) Mean±SD
Control (n=30)	220.75±2.9	7265.25±20.6	2.86±0.5	368.34±1.1
Endocrine / Reproductive System Region (n=30)	384.60±4.3	5087.61±10.6*	1.10±0.3*	436.50±1.3*
Lumbosacral Region (n=30)	430.07±4.3	5760.03±46.7**	1.54±0.5	338.07±1.1*

Mann-Whitney U

* Difference between experimental and control group; $p < 0,05$

** Difference between Endocrine / Reproductive System Region and Lumbosacral Region

Mean±SD: Mean±Standard Deviation



VEGF: Vascular Endothelial Growth Factor; MMP: Matrix metalloproteinases; TSP: Thrombospondin

Figure 1: The distribution of the levels of angiogenic and antiangiogenic markers of the experiment group with reflexology on the endocrine system and reproductive organs (Group 1) and the experiment group with reflexology on the lumbosacral region (Group 2) and the control group of women.

DISCUSSION

Breast milk, which perfectly meets the physiological and psychosocial needs of the baby in the first six months after birth, is an important factor in the establishment of mother and baby bond. Feeding the baby exclusively with breast milk for the first six months, and continuing breastfeeding with supplementary foods after the sixth month until the end of the age of two

provide numerous benefits for the mother and the baby, and also have positive effects on advanced life health^{15,16}. In this study, which was conducted to examine the effect of reflexology on angiogenic factors in women giving birth, it was seen that reflexology has a positive effect on angiogenic factors and may positively affect breastfeeding.

Reflexology, which has stimulating effects on the central nervous system and mood and causes deep relaxation, regulates blood flow by reducing mental stress and pressure¹⁷. Thanks to these effects, it also plays an important role in the lactation process. According to studies, reflexology has been found to be effective in increasing the volume of milk released by accelerating milk production and in maintaining lactation, as well as initiating and maintaining lactation, increasing breastfeeding success after birth in mothers who give birth by cesarean section as in mothers who have normal birth¹⁸⁻²⁰. Angiogenesis is the formation of new vessels from the existing vascular structure. Endothelial cells that form the basis of angiogenesis mechanism; In addition to containing the main veins and genetic information forming the capillary network, it also forms the wall structure of the capillary vessel with pericytes. In a healthy and adult human, the cycle and angiogenesis of endothelial cells occurs very slowly (3-12 months), while angiogenesis occurs only under certain conditions such as wound healing, embryo development or formation of the corpus luteum structure in a very short time²¹. Breast milk production that occurs in the postpartum period is also included in this process.

VEGF is a potent angiogenic factor and described as an essential growth factor for vascular endothelial cells²². Studies have found that VEGF and VEGF receptors increase in breast milk, especially in the early postpartum period. Especially in preterm births or on the days when colostrum is secreted, VEGF and receptor concentrations in early milk (3rd day of lactation) were found to be lower than the concentration in mature milk (28th lactation), and it was also reported that VEGF concentration started to decrease from the 3rd day of lactation^{23,24}. In this study, when the VEGF levels are compared in the control group and the reflexology groups, although there is no statistical increase, a significant increase is observed. In this respect, it can be said that reflexology application is

important in order to increase milk release and initiate breastfeeding, especially in women who give birth by preterm birth or cesarean section. Metallinou et al. (2019) reported that MMP-9 enzyme, which is one of the gelatinases, was found in colostrum after birth, and it was found that its concentrations decreased after the 2nd day²⁵. In the same study, given the ability of gelatinases from MMP species to act as a bacteriostatic agent and mucosal healing activity in the gastrointestinal tract, it is emphasized that early breastfeeding of newborns is important in terms of obtaining adequate colostrum. In this study, a statistical decrease is observed in the level of MMP, and it is expected to increase especially in the last postpartum days as it plays a role in the postpartum reproductive organs to reach their original dimensions.

Endostatin has been shown to specifically inhibit endothelial proliferation, migration and tube formation and induce apoptosis in endothelial cells²⁶. In this study, it is thought that the significant decrease in endostatin level is related to the increase in VEGF level and milk production during lactation.

Thrombospondin has been shown to inhibit the proliferation of endothelial cells in many different tissues and destabilize the relationship between endothelial cells. TSP 1 and TSP 2 are anti-angiogenic proteins modulated by hypoxia and oncogenes; particularly, TSP 1 expression is inversely proportional to tumor stage. Tumor cells transfected with the TSP-2 expression vector showed that tumor vascular density and size were significantly reduced despite the secretion of strong angiogenic factors such as VEGF; even TSP2 has been shown to be a stronger anti-angiogenic factor than TSP-1²⁶. In this study, no statistical difference was found in thrombospondin level.

Compared to the control group, there is an increase in VEGF concentration, a statistical decrease in MMP and Endostatin levels in the reflexology group applied to the lumbosacral area and the endocrine system / reproductive organs group, and no significant change is observed in TSP. Although there is no statistical significance when the lumbosacral region is compared with the endocrine / reproductive system, a significant decrease is observed in the level of TSP. The limitations of this study. The fact that the study was conducted in a single hospital and 90 women in the postpartum period participated in the study are the most important limitations of the study. Also reflexology was used two regions in foot instead of all foot in this study. There are no

sufficient studies examining the effect of reflexology application on angiogenic factors that change during lactation. Therefore, it is important to support research on the subject and contribute to the literature.

CONCLUSION

As a result, in this study, it was recognized that reflexology applied to the region where the endocrine systems/reproductive organs and lumbosacral are located is more effective in lactation period and breast milk production. According to the angiogenic factors increase especially during the lactation process, it is expected that reflexology will increase breast milk in women and also women will relax and experience a comfortable breastfeeding process. Considering the benefits of breastfeeding in terms of maternal and infant health, it is recommended to apply reflexology to all women starting in the early postpartum period. Thanks to reflexology, babies will be provided with breast milk for the first six months, and thus, more healthy babies will be raised with a stronger immune system.

Abbreviations

VEGF, Vascular endothelial growth factor; VPF, vascular permeability factor; MMP, Matrix metalloproteinases; Zn, zinc; Ca, calcium; BBB, blood-brain barrier; TSP, thrombospondin; MCBU, Manisa Celal Bayar University; BMI, body mass index; ELISA, Enzyme-Linked Immuno Sorbent Assay; SPSS, Statistical Package for the Social Sciences,

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