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PELVİK ADEZYONLARDAKİ SİNİR LİFİ VARLIĞININ KRONİK PELVİK AĞRI ÜZERİNDEKİ ETKİSİNİN DEĞERLENDİRİLMESİ: PROSPEKTİV KOHORT ÇALIŞMASI

EVALUATION OF THE EFFECT OF NERVE FIBER PRESENCE IN PELVIC ADHESIONS ON CHRONIC PELVIC PAIN: PROSPECTIVE COHORT STUDY

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ÖZ

Giriş: *Gebelik sırasındaki abdominopelvik ağrı, kadın doğum uzmanlarının karşılaştığı en yaygın sorunlardan biridir. Özellikle batın içi yapışıklıkları olan hastalarda gebelikte uterus büyümesi sırasında artan gerginliğe bağlı olarak kronik pelvik ağrı gelişebilir. Sezaryen ameliyatı sonrası batın içi yapışıklıkların gelişimi ve komplikasyonları ile ilgili veriler oldukça azdır. Bu çalışmanın amacı uyarı iletme potansiyeli olan sinir liflerinin pelvik adezyonlardaki varlığını incelemek ve adezyonlardaki sinir liflerinin sezaryen olan hastalarının klinik parametreleriyle korelasyonunu değerlendirmektir.*

Gereç ve Yöntem: *Bu çalışma prospektif kohort çalışması olarak planlandı. 12-16. Gebelik haftaları arasındaki hastalarda demografik özelliklerle beraber dismenore, dizüri ve kabızlık gibi klinik şikayetleri sorgulandı. Ağrının şiddeti standart bir anket ve Visual Analog Skalası kullanılarak değerlendirildi. Ağrı değerlendirmesi ikinci trimesterde (24-28 haftada) ve üçüncü trimesterde (36-38 haftada) tekrarlandı. Herhangi bir sebeple sezaryen doğum yapan 194 hasta karın içi yapışıklıklar açısından değerlendirildi. Ameliyat sırasında pelvik adezyonlara adezyektomi uygulandı. Histolojik kesitlerde miyelinli ve miyelinsiz sinir liflerini gösterebilmek için spesifik polyclonal rabbit anti-protein gen 9.5 (PGP9.5) antikoru ile immünohistokimyasal olarak boyandı. Nöron pozitifliği olan veya olmayan hastalar ağrı şiddeti açısından değerlendirildi.*

Bulgular: *Hastaların %29,5'inde pelvik adezyon izlendi. Pelvik adezyonlarda PGP9.5 ile boyanmış sinir lifleri hastaların %31,1'inde saptandı. Adezyonlarda sinir lifi görülen hastalarda ağrı semptomları daha yüksek saptandı. Ağrı olmayan 5 (%19,2) hastada pozitif lif bulundu. Sinir lifi pozitifliği pelvik adezyonlarla ilişkiliydi, fakat ağrı şiddeti ile ilişkili değildi.*

Sonuç*: Bu çalışma pelvik adezyonlarda duyu siniri lifi varlığına dair kanıtlar sunmakta olup, bu yapıların uygun stimülasyondan sonra ağrıya neden olabileceğini düşündürmektedir.*

SUMMARY

Introduction: *Abdominopelvic pain during pregnancy is one of the most common problems that obstetricians deal with. Especially in patients who have intraabdominal adhesions, chronic pelvic pain may develop due to increased tension during adherence with uterine growth during pregnancy. Data concerning the development of intraabdominal adhesions and their complications after caesarean surgery is quite scarce. The purpose of the*

present study was to evaluate the presence of nerve fibres in pelvic adhesions potentially capable of conducting stimuli and correlation of nerve fibres in adhesions with clinical parameters in female patients undergoing caesarean section.

Materials and Methods: *This study was planned as a prospective cohort study. The patients were evaluated between 12-16 weeks of gestation; and demographic features and clinical complaints such as dysmenorrhea, dysuria and constipation were questioned. The pain symptom severity was recorded with a standard questionnaire and Visual Analogue Scale (VAS). The pain assessment was repeated at second trimester (at 24-28 weeks) and third trimester (at 36-38 weeks) of gestation. The abdominal cavity of 194 women who underwent caesarean section for different reasons was evaluated in terms of adhesions. Pelvic adhesions were collected during surgery and histological sections of adhesions were stained immunohistochemically with specific polyclonal rabbit anti-protein gene 9.5 (PGP9.5) antibody to show myelinated and unmyelinated nerve fibres. Patients with or without neuron positivity were evaluated for pain severity.*

Results: *Pelvic adhesions were observed in 29.5% of the patients. PGP9.5-stained nerve fibres were detected in pelvic adhesions in 31.1% of the patients. Pain symptoms were higher in the patients who had nerve fibres in adhesions (P<0.001). Positive fibres were found in 5 (19.2%) patients who did not have pain.*

Conclusion: *The present study reports the evidence for sensory nerve fibre presence in pelvic adhesions, which suggests that these structures might cause pain following appropriate stimulation.*

INTRODUCTION

Adhesions are described as the fibrous tissue bands, that may be vascular or avascular and linking up the serosal and/or nonserosal surfaces of the internal organs and abdominal wall where there should be no adhesion (1).

Pelvic ınflammatory disease , previous surgery, endometriosis, foreign bodies (suture, gas, glove powder, mesh), irradiation and ınflammatory bowel disease are known risk factors of pelvic adhesions (2). In a study that was conducted on 752 cadavers that had undergone laparotomy, the rate of detecting adhesion was found to be 67% (3). Animal studies revealed that adhesion formation occurs predominantly within the postoperative first week (4). The most common sites for adhesion formation are ovaries and fallopian tubes (5). Intraabdominal adhesions usually do not cause any symptoms; however, they may cause chronic pelvic pain and intestinal obstructions in some patients, and secondary infertility in females (6). It remains controversial how adhesions contribute to pelvic pain. Nevertheless, peritoneal adhesions are thought to be potentially capable of conducting stimuli and are considered among pelvic pain causes (7).

The abdominal wall is innervated with somatic nerves (T5-L2), and stimuli is conducted by motor and sensory fibres. Parietal peritoneum is rich in pain receptors that transmit pain stimuli to the central nervous system (8). Adhesions contain visceral peritoneal tension receptors and receives afferent nerve fibres from the spinal cord. Post-surgical pelvic and abdominal adhesions have been shown to be rich in nerve fibres. On the other hand, peritoneal adhesions can cause pain indirectly by limiting organ movements or causing enlargement. In this respect, neighbouring organ or abdominal wall smooth muscle tension receptors are stimulated. It has been hypothesized that distension, hypoxia, and inflammation stimulate sensory borders in the adhesions, which, in turn, trigger the cascade of pain stimuli. In addition, it can cause pain by stimulating stretch-sensitive fibres directly on the tension of the adhesions (9).

Some early studies reported pain relief following surgical adhesiolysis (10). Some mapping studies support the hypothesis that adhesions generate pain themselves (9). In a previous study conducted by Herrick et al., 29 patients undergoing laparotomy for various conditions were evaluated and adhesions were collected. They reported that the adhesions had vascularization; and in nearly two-thirds of the patients, both myelinated and non-myelinated nerve fibres were present (9). Some immunobiological studies also proved nerve fibre presence in adhesion tissue of patients both with and without pain, which suggest that there is no correlation between presence of neural tissue in adhesions and pain (11).

Abdominopelvic pain during pregnancy is one of the most common problems that obstetricians deal with. Especially in patients who have intraabdominal adhesions, chronic pelvic pain may develop due to increased tension during adherence with uterine growth during pregnancy. Data concerning the development of intraabdominal adhesions and their complications after caesarean surgery is quite scarce (12).

The aim of this study was to evaluate the nerve fibre presence in pelvic adhesions and the correlation with abdominopelvic pain that occur during pregnancy follow-up in women who underwent caesarean surgery.

MATERIALS AND METHODS

The study was approved by the Local Ethics Committee of University of Health Sciences Sisli Hamidiye Etfal Training and Research Hospital in 2015 (approval number: 2015/1136). We conducted the prospective study with 194 women who had undergone caesarean section from September 2014 and April 2016 at a single tertiary centre. Informed consent forms were received from all patients before the study commenced.

The patients were initially assessed during the first trimester between 12-16 weeks of pregnancy. Patients' characteristics including age, gravida, parity, history of dysmenorrhea, dysuria, constipation, previous caesarean were recorded. Patients with a history of chronic pelvic pain, surgery other than caesarean, radiotherapy, endometrioma or endometriosis, pelvic inflammatory disease or tuboovarian abscess and who had psychosomatic pain were not included in the study. Patients who diagnosed with myomas or ovarian cysts during pregnancy and those who delivered vaginally were excluded from the study

The pain symptom severity was recorded with a standard questionnaire and VAS by a blinded observer. The pain scale was divided into 10 sub-levels. 'No pain' was shown on the left of the scale, and 'the maximum pain you could imagine' on the right (13). The pain assessment was repeated at second trimester (at 24-28 weeks) and third trimester (at 36-38 weeks) of gestation. The abdominal cavity of 194 women who underwent caesarean section for different reasons was evaluated in terms of adhesions after the infant was delivered. Sites of adhesions were divided into regions as left tuboovarian, right tuboovarian, pouch of Douglas and bladder. The presence of endometriosis, myomas or cysts were recorded and these patients were excluded also. Tissue specimens from the pelvic adhesions were collected during surgery, were washed in saline solution (pH 7.4), and fixed in paraformaldehyde 4% solution at room temperature until processing.

Histological sections of adhesions were immunohistochemically-stained with specific polyclonal rabbit anti-protein gene 9.5 (PGP9.5) to show myelinated and unmyelinated nerve fibres. Patients with or without neuron positivity were evaluated for pain severity. Paracetamol (Parol 500 mg tablets, Atabay AŞ, Istanbul, Turkey) was administrated orally at a dose of 500 mg/day per 8 hours. No additional pain killer medications were given to any of the patients.

Statistical analysis

Statistical Package for the Social Sciences Version 20.0 (IBM, New York, USA) was used to perform statistical analyses. Data are presented as means and standard deviation. The Pearson Correlation, Spearman analysis, was employed in the analysis of the correlation between nerve fibre presence in adhesions and pain severity. P value lower than 0.05 was considered as statistically significant.

RESULTS

The average age of the included and evaluated patients was 29. Pelvic adhesions were observed in 57/194 (29.5%) of the patients. Histological evaluation revealed that nerve fibres and fibrosis were present in 21.8% and 17.6% of the peritoneal adhesions examined, respectively.

The adhesion presence was associated with a higher average VAS. Pelvic adhesions were most commonly detected in the right adnexal region. A statistically significant relationship was found between the presence of adhesions and the pain scale ($p<0.001$), (Table 1). Patients with nerve fibres in their adhesions significantly more frequently reported pain located in the lower right abdomen, as compared to those without nerve

fibres in the adhesion tissue (p<0.001), (Table 2). The total number of caesarean sections and the presence of nerve in adhesions were highly correlated (p<0.001), (Table 3). In addition, pre-pregnancy and all-trimester pain values were found higher in patients with previous caesarean section, compared to first caesarean section patients. The presence of adhesion on the anterior wall of the bladder was determined to be higher and different in patients with previous caesarean section compared to the first section patients . Pain was more common in all periods of pregnancy in those who had C/S before.

Table 1. The relationship between the presence of adhesions and the pain scale

Correlation levels	Presence of adhesion	P value
Pre-pregnancy pain value	0.429	0.000*
First trimester pain value	0.611	0.000*
Second trimester pain value	0.382	0.000*
Third trimester pain value	0.530	0.000*
Nerve presence	0.920	0.000*

Correlation levels:
0.00-0.20 →very low
0.21-0.40 →low
0.41-0.60→medium
0.61-0.80→high
0.81-1.00→very high
* Statistically significant

Table 2. Relationship between nerve presence and pain site, adhesion site

Nerve presence					
		Total (%)	Nerve presence (%)	Non-nerve presence (%)	Pvalue
Pain site	Total	100	100	100	
	Left low abdomen	9.3	11.9	8.6	0.000*
	Right low abdomen	22.3	45.2	15.9	0.000*
	Suprapubic	12.4	33.3	6.6	0.000*
	Back-reflected, rectal	5.7	19	2	0.000*
	Absence	53.9	0	68.9	0.000*
Adhesion site	Left adnex	7.3	33.3	0	0.000*
	Right adnex	8.8	40.5	0	0.000*
	Bladder front Wall	2.6	9.5	7	0.000*
	Douglas	3.6	16.7	0	0.000*
	Absence	77.7	0	99.3	0.000*

Correlation levels:
0.00-0.20 →very low
0.21-0.40 →low
0.41-0.60→medium
0.61-0.80→high
0.81-1.00→very high
* Statistically significant

Table 3. Relationship between nerve presence and other variables

Correlation levels	Nerve presence	P value
Total number of caesarean sections	0.729	0.000*
Previous caesarean section	0.582	0.000*
Pre-pregnancy pain value	0.510	0.000*
First trimester pain value	0.679	0.000*
Second trimester pain value	0.439	0.000*
Third trimester pain value	0.608	0.000*

Correlation levels:
0.00-0.20 →very low
0.21-0.40 →low
0.41-0.60→medium
0.61-0.80→high
0.81-1.00→very high
* Statistically significant

Table 4. Relationship between nerve proliferation, pre-pregnancy pain value assessment, third trimester pain value assessment and other variables

Correlation levels	Nerve proliferation	P value	Pre-pregnancy pain value	P value	Third trimester pain value	P value
Fibrosis	0.733	0.000*	0.466	0.000*	0.504	0.000**
Age	0.204	0.004*	0.113	0.118	0.062	0.389
Gravidity	0.040	0.581				
Parity	0.076	0.293	0.068	0.344	0.034	0.637
Total number of caesarean sections	0.704	0.000*	0.395	0.000*	0.394	0.000*
Previous caesarean section	0.567	0.000*	0.341	0.000*	0.338	0.000*
Dysmenorrhea	0.517	0.000*	0.277	0.000*	0.441	0.000*
Dysuria	0.319	0.000*	0.186	0.010*	0.328	0.000*
Constipation	0.332	0.000*	0.227	0.002*	0.094	0.192
Pre-pregnancy pain value	0.495	0.000*			0.287	0.000*
First trimester pain value	0.630	0.000*	0.586	0.000*	0.491	0.000*
Second trimester pain value	0.378	0.000*	0.290	0.000*	0.505	0.000*
Third trimester pain value	0.562	0.000*	0.287	0.000*		
Nerve proliferation			0.495	0.000*	0.562	0.000*
Nerve presence			0.510	0.000*	0.608	0.000*

Correlation levels:
0.00-0.20 →very low
0.21-0.40 →low
0.41-0.60→medium
0.61-0.80→high
0.81-1.00→very high
* Statistically significant

Among a total of 194 women, 35 (57.4%) had dysmenorrhoea complaints and related pain symptoms, and no pain symptoms were determined in 26 (42.6%). For the 29 women who had adhesions, 17 (58.6%) had pain symptoms and 12 (41.4%) had no pain symptoms.

PGP 9.5-stained nerve fibres were detected in pelvic adhesions in 31.1% of women. Pain symptoms were more frequent in women who had nerve fibres in adhesions. In women without pain, positive fibres were detected in only 5 (19.2%) women.

Nerve proliferation was associated with fibrosis, age, caesarean number, dysmenorrhea, dysuria, constipation, pre-pregnancy and all trimester pain scores. Conversely, there was no correlation between nerve proliferation and either gravidity or parity (Table 4).

There was a significant relationship between pre-pregnancy pain and nerve proliferation, nerve presence, fibrosis, total number of caesarean sections, dysmenorrhea, dysuria, constipation and pain at all trimesters. As shown in Table 4 gravidity, age and parity were not associated with pre-pregnancy pain scores. Similarly, in the study, it was observed that third trimester pain scores were highly correlated with nerve proliferation, nerve presence, pre-pregnancy pain value, fibrosis, total number of caesarean sections, dysmenorrhea, pain values of first and second trimester. However, there was no significant correlation between age, gravidity, parity, constipation and third trimester pain (Table 4).

Pre-pregnancy pain and pain at all trimesters were associated with nerve presence and it is shown in Table 3.

Eventually, there was a statistically significant relationship between the presence of nerve fibres and the location of pain and adhesion. In cases where adhesion was located in the anterior bladder wall, the percentages of nerve fibre presence was significantly different and higher (Table 2).

DISCUSSION

The relation between pelvic pain and amount of adhesions is questionable. In this study pain symptoms were detected higher in women who had nerve fibre presence in adhesions. The nerve fibre positivity was associated with pelvic adhesions but not with pain severity.

It is known that the sensory nerve presence in adhesions does not necessarily involve chronic abdominopelvic pain. These nerves might not be functional or need a series of inducing stimuli to transmit pain sensations, which is the case in visceral peritoneum (14). The presence of sensorial nerves in adhesions may not always cause abdominopelvic pain. Because the nerves in these adhesions may not be functional, or may not have adequate stimuli to create the sense of pain (14).

In 2001, Sulaiman et al. conducted a study to evaluate the nerve fibre distribution and type in human peritoneal adhesions. They stated that all adhesions contain nerve fibrins and thin non-myelinated neurons in adhesions could transmit pain stimuli. In the same study it was also noted that not all the patients had chronic pelvic pain which was probably related to peritoneal pathology, organ mobility and psychosomatic findings (15). The presence of sensory nerves in the adhesions in the peritoneum in our study supports the findings in the literature. It is possible to speculate that thin myelin-free fibres play roles in transmitting these pains although pain is not shown directly physiologically. However, not all patients in our study complained of chronic pelvic pain. However, the factors like another peritoneal pathology, the mobility of organs, presence of psychosomatic symptoms may have caused this result.

In studies that investigate the etiology of pelvic pain, the most common intraoperative findings are endometriosis and pelvic adhesions (16). As a result of a series that investigated the etiology of chronic pelvic pain laparoscopically, it was reported that 35% of the patients did not have any pathologies, and 24% did not have any adhesions (range: 0 to 54%) (17). Unlike this study, peritoneal adhesions were shown in 17% of women who underwent laparoscopy for other reasons, and who did not suffer from chronic pelvic pain (18). However, these two studies were planed retrospectively, and the long-term follow-up of the patients was not performed. In this prospective study, which included 194 patients, we did not include patients who had a history of chronic pelvic pain, and as a result, we observed the frequency of pelvic adhesion to be 29,5%. Therefore, we can conclude that not all adhesions will cause pelvic pain.

Adhesions can be observed in various morphologies including filmy, vascularized and cohesive (19). Although the prevalence of intraabdominal adhesions varies, it is detected during laparoscopy in many patients who have chronic pelvic pain. The risk factors of intraabdominal adhesions are pelvic inflammatory disease, previous abdominal operation history, endometriosis, and history of perforation in visceral organs (20). The relation between adhesions and chronic pelvic pain is still controversial. For this reason, performing adhesiolysis in chronic pelvic pain is also controversial.

Chan and Wood showed that adhesiolysis alleviated the symptoms in patients who had chronic pelvic pain; however, this study did not have any no control group (21). Peters et al. divided 48 patients who had pelvic adhesion into 2 groups, and applied adhesiolysis to one group, and applied expectant treatment to the other group. Then, they called all the patients for a follow-up after 9-12 months, and re-evaluated the pelvic pain. However, no significant decreases were detected in pain in both groups (22). In another multicentre study that involved 116 patients, no differences were detected between the pain scores of the patients undergoing laparoscopy, adhesiolysis, and conservative treatment (23). In this study, a total of 17 (58%) of the 29 patients who had adhesion had pain symptoms, and 12 (41.4%) patients had no pain. Based on the findings of this study, we believe that patients who have adhesions are more likely to experience pain. For this reason, surgical adhesiolysis might be considered as an option in patients who have chronic pelvic pain because of adhesions during follow-ups. The limitations of the study were that the nerve fibres were likely to be caused by adjacent parietal or visceral peritonea as well as adhesions.

As a result, in this study, it was determined that there is a relation between the adhesions determined during the operation and the pain complaints of the patients. Not all patients in the study complained of pelvic pain. Although intraabdominal adhesions cause pain complaints via nerve conduction, it must be kept in mind that

other factors like peritoneal pathologies, psychosomatic events, etc. may also be effective.

There are some limitations of our study. Additional risk factors such as race, weight, smoking and alcohol were not included in the study.However, it would be difficult to recruit enough patients in that kind of study.

CONCLUSION

The present study reports the evidence for sensory nerve fibre presence in pelvic adhesions, which suggests that these structures might cause pain following appropriate stimulation.

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