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EDITORIAL

Dear Colleagues;

The Journal of Pelviperineology has turned into a journal that is being accepted and respected on different scientific platforms day by day. As an extension of this, we have been accepted to China Knowledge Resource Integrated (CNKI), the Chinese medical directory, and then TR Indexation, the Turkish medical directory.

CNKI, which started operating in 1988; stands out as the largest academic database of Chinese origin, indexing academic journals, documents compiled from major newspapers, master's and doctoral theses and full-text annual books. It contains articles from a total of 11395 journals in fields such as basic sciences, engineering, technology, medicine, political science, economics, law, history and literature. CNKI also provides online training in different fields. It also serves 1.600 institutes from 60 different countries and has 20 strategic partners to establish a global network. In 2021, it reached 16 million daily clicks with 200 million active users, and its academic content was downloaded 2.33 billion times. Its users range from universities, research institutes, government think tanks, businesses and hospitals to public libraries.

Regarding the TR Indexation; it is the first database which has been functioning since 1992. The TR Index being created by ULAKBIM consists of journals in the main fields of Science and Social Sciences, and subfields of Dentistry, Pharmacy, Engineering, Basic Sciences, Health Sciences, Veterinary Medicine, Social Sciences and Humanities. TR Index can be scanned through the web page (https://trdizin.gov.tr/) since August 2000.

The TR Index includes 1.657 journals, 511.043 studies and 21.891 projects. In this context, it is Türkiye's largest scientific guide.

In conclusion, The Journal of Pelviperineology has been indexed in EBSCO, GALE, Index Copernicus, J-Gate, ProQuest, Scopus, TR Index, CNKI.

Naturally, this success has been achieved with the contributions of our authors, referees and readers, without them this success would have never been realised.

Stay healthy,

Prof. Dr. Ahmet Akın SiVASLIOĞLU

Editor in Chief

Interview with Prof. Lewis WALL by Prof. Peter PETROS

You are known for your longstanding interest in and advocacy for the health problems of women in Africa, in particular the obstetric fistula.

Yet, your initial degree was in anthropology. You graduated from the University of Kansas with a B.A. in anthropology and history "with highest distinction." What caused you to study anthropology?

I have always seen history and anthropology as complementary to one another. Both attempt to understand societies in similar ways--but history does so in a diachronic fashion and anthropology does so in a synchronic way--so to me, they were always only different aspects of the same discipline, slightly different ways of looking at the same problems.

You went on to study social anthropology as a Rhodes Scholar at the Institute of Social Anthropology and The Queen's College, Oxford University. You achieved the degree of D.Phil. What was the background to this endeavor, and to your D. Phil.?

My original intention at Oxford was to pursue a degree in Egyptology, oddly enough. Ancient history, archaeology, and anthropology all fit together well, but after a couple of months I found I was more interested in the broader anthropological questions than in the narrower strictly Egyptological ones, so I shifted to the Institute of Social Anthropology, where I did the Diploma in Social Anthropology and then wrote a post-graduate Bachelor of Letters (B.Litt. -a degree that no longer exists!) thesis on the comparative mythologies of the people of the upper Nile basin (Anuak, Shilluk, Dinka and Nuer).

But I was starting to become tired of the academic infighting that I saw around me. Henry Kissinger once remarked something to the effect that "academic fights are so vicious because the stakes are so low." That resonated with me. I was becoming more interested in the interactions between society, health, disease, and medical care, so I made a contact at the Liverpool School of Tropical Medicine and went up to see if they had any projects in which my participation might be useful.

The drawback was that they had no budget for an anthropologist. I would have to fund my own way. I came back to the US after having defended my B.Litt. thesis, worked in a pizza restaurant for a few months, applied for various grants and as I realized that medicine was appealing to me more and more, I re-enrolled at the University of Kansas to take the courses that were absent from my undergraduate program of study: Physics, chemistry, biology, etc.

As I was walking out the door of my dormitory to take my final exam in second semester general chemistry, I had a phone call saying that I had been awarded a Fulbright-Hayes Fellowship to do fieldwork!

To make a long story short, I did go to Nigeria and linked up with the Department of Community Medicine at Ahmadu Bello University in Zaria. They had a rural teaching hospital in a town called Malumfashi and I set up a base there I scouted a number of villages in the surrounding countryside, found one to my liking, moved in, and started to do anthropological things: Asking questions about health and disease and causation, etc. It was fascinating and I learned a lot. I lived there for nearly two years, totally immersed in rural African life.

I realized two important things over this period of time. First, rural African villagers needed doctors more than they needed anthropologists, and second, it would probably be a lot easier to put food on the table with a medical, as opposed to an anthropological, degree. So I decided to go "all in" on the attempt to go to medical school.

I went from living in a rural African village to an organic chemistry lab at the University of Kansas in six weeks. It was pretty jarring. I was also trying to write my doctoral dissertation. A few weeks after my arrival back in the States, I met a beautiful young English woman named Helen Pratt, who had arrived at the University of Kansas to do a master's degree in botanical biochemistry in the lab of a faculty member I had known. I fell hopelessly in love with her and eventually persuaded her to marry me.

We got married at the end of the fall semester that I started medical school at the University of Kansas School of Medicine.

Medical school was a trying experience. Intellectually, it was dominated by the rote learning of "facts" about anatomy, physiology, and pathology-a far cry from being a doctoral student at Oxford! I was also trying to write my doctoral dissertation while being a full-time medical student. That didn't work. I took a leave of absence after the first two (pre-clinical) years of medical school to complete the writing up, then jumped into my clinical rotations. The end result was that I was six months out of sync with the system. We made up for it by going to Zaire (now the Democratic Republic of the Congo) to work in a mission hospital and also to work in London at Queen Charlotte's Maternity Hospital and the Chelsea Hospital for Women. I then landed in Durham, NC, to begin my ob-gyn residency at Duke University Medical Center.

Your father was a well-known obstetrician in Kansas. Can you tell us a little about him?

My father, Dr. Leonard A. Wall, was quiet, sympathetic, hardworking, dedicated to his patients, a man of great integrity and quiet compassion.

Dad grew up on a farm in the Oklahoma panhandle, a flat desolate area in western Oklahoma.

He went to a one-room country schoolhouse. He went to officer's school and became a second lieutenant and a pilot. He married my mother- his high school sweetheart- in October, 1944, just a few days before he was shipped overseas to England, where he flew B-17s as a co-pilot doing bombing runs over Nazi Germany. His plane was shot down over Germany in early 1945. Dad was the last man who got out alive. He bailed out and opened his parachute just as the plane exploded, killing the pilot who was just about to jump from the cockpit.

Dad was listed as "missing in action and presumed dead," but in reality he was a prisoner of war. There were several anxious months for my mother before they found out he was actually alive

He came back from the war in poor health, as you can imagine, but got back into the University of Oklahoma, did well, and was admitted to the medical school in 1947.

He became the "obstetrician's obstetrician" in Kansas City, where he finally settled into practice. A truly great man. I miss him terribly.

What inspired you to specialize in Ob-Gyn?

Initially I had no intention whatsoever of going into medicine at all. It was my experiences in Africa doing field research that started to change my mind.

You subsequently specialized in urogynecology and reconstructive pelvic surgery. Why reconstructive pelvic surgery?

When I started my residency training in 1983, urogynecology was only a dimly lit field of clinical practice that had not yet started to get much clinical traction. Duke University had one of the best pelvic surgery programs in gynecology and that also helped spur my interest. I managed to get a fellowship position in London with Stuart Stanton and then later in Manchester, England, with David Warrell, two of the leading pioneers in the field back when there were almost no fellowship training opportunities in the United States.

Can you outline the highlights of your subsequent career?

It was pretty much a standard academic career I was a very good student and the academic pathway appealed to me. I really enjoyed being part of academic units at universities around the county. I got to travel, to see the world, and to have a good livelihood to boot.

Early in your career, you achieved a degree in bioethics. Your writings contain a powerful ethical tone. Indeed, you have written extensively on injustice, in particular, in Africa. You quote from the stoic philosophers Marcus Aurelius, Seneca, and Epictetus as part of your sign-off in your emails. What were the influences which drove you to your interest in bioethics?

I have always been interested in the ethics of medical practice, largely because I wanted to "be a good doctor." Most of us get our ethical grounding in practice from emulating role models of doctors whom we "want to be like."

When I was on the faculty of the School of Medicine at the Louisiana State University Medical Center in New Orleans, our Department was wracked by a major scandal involving one of the professors.

After that experience, I felt like I had to do a deep dive into medical ethics just for my own benefit, to get better analytical tools and a better grounding in the literature of the field.

Was your upbringing a factor? If so, can you elaborate.

I grew up in a solidly Christian home with solid values and a mandate to be attentive to the welfare of others. I brought that background with me into medicine.

You end your correspondence with quotes from Stoic philosophy. Indeed, the key precepts of stoic philosophy are very much part of your writings. When did you become interested in stoic philosophy? How has it influenced your career and your writings?

As I noted earlier, my undergraduate degree had a strong focus on ancient history. The Stoics were the leading philosophers of the later Graeco-Roman world. I got exposed to them early in my undergraduate career, but I found them increasingly interesting and influential as I confronted the problems at LSU and began exploring bioethics. They have so much to teach us today about how to live in a troubled world and to not go crazy in the process.

You are well known for your work Obstetric Fistula. You founded the Worldwide Fistula Fund in 1995, a not-for-profit public charity dedicated to providing care for women who have developed obstetric fistulas from prolonged obstructed labour. You founded a 42 bed fistula hospital in Niger. Can you tell us more about the fistula hospital, how it works and how it was funded?

I had spent a lot of time in Africa in the 1970s doing anthropological field work, so I had a pretty good grasp of what life in rural Africa was like. The man who persuaded me to join him on the faculty at LSU, the late Dr. Tom Elkins, was a pioneer in urogynecology, a leader with a strong interest in medical ethics He was incredibly supportive of those who wanted to work in Africa in this particular field and he facilitated my interest in this very much. Tom was instrumental in setting up the ob-gyn residency training programs in Ghana, and I was very much involved in that.

In 1994 I went to Ethiopia for the first time and spent time with Dr. Catherine Hamlin at the world-famous fistula hospital that she and her late husband, Dr. Reg Hamlin, had built in Addis Ababa. That was inspirational and motivating for me. I wanted to try to replicate something similar in West Africa where I had worked as an anthropologist, so we founded The Worldwide Fistula Fund in 1995.

To make a long story short, the hospital in Danja, Niger, was really made possible by my friend, the New York Times columnist Nicholas Kristof. Nick's column raised over $500,000 for the hospital. The hospital operates in partnership with a Christian missionary organization, SIM, and is funded by donations through SIM and through The Worldwide

Fistula Fund. It has been a challenge, but it has done a great deal of good, treating hundreds of women with life-altering surgeries since it was founded and providing them with the social support they need to reintegrate back into society after surgery.

There are said to be 2-3 million women with fistulas in Africa? How can this huge number be reduced? You became politically active in trying to bring more human and material resources to prevent fistula problems. Can you elaborate on your own endeavours? Where are things now and how you see the future?

To quote a famous Stoic -Lucius Annaeus Seneca- "The larger part of goodness," he said, "is the will to become good". That is to say, you have to care, you have to want to make changes, in order to achieve change. Translated into reality, it means that a problem like this can only be solved by political will and to muster the political will, people have to care about poor women in Africa and Asia where the problem is greatest.

Obstetric fistula is such an awful malady-a labor that lasts 3 or 4 days resulting in a stillbirth and horrible birth injuries. People in the industrialized West don't understand that such injuries are even possible, much less that they occur with such alarming frequency in the poor parts of the world.

The solution to this problem is universal access to high quality obstetrical care, with skilled birth attendants at every delivery, prompt referral of prolonged labors, and paying attention to the healthcare needs of the world's women. Making this happen is still a very low priority in most poor countries that are trying to develop better economies. Maternity care is one of the most important investments that a society can make in its future. As my dad hammered home to me, the most important thing in life is to be born wanted and loved. We need to push this to the forefront of the world's consciousness.

There is also a need in areas where fistulas are most prevalent to create specialist centers that can treat the whole range of problems faced by women with obstetric fistulas. The strategy needs to be "treating the whole woman," not just "treating the hole in the woman". I have been fortunate to be involved in setting up specialist fistula centers in Jos, Nigeria; in Danja, Niger; and to work with the Hamlin Fistula hospitals in Ethiopia. I have also been involved in creating a new fistula center--the Terrewode Women's Community Hospital--in Soroti, Uganda, where I am on the Board of Governors, and also to work with Dr. Itengre Ouedraogo in Burkina Faso as he sets up a new fistula center there.

There have been major disruptions with wars in Ethiopia. What was the fate of the fistula hospitals and other humanitarian facilities? Can you tell us how all this has impacted on the care of the fistula women and the medical facilities themselves.

The regional war in northern Ethiopia -it is far bigger than a so-called "civil war"- has had a devastating impact on the population. At least 500,000 people have died, millions have been displaced, and millions more are at risk of starvation. At least 90% of the medical and educational infrastructure in Tigray has been destroyed. The healthcare system does not function so fistulas, which had almost been eliminated in this part of Ethiopia, have made a comeback. Not just because women with obstructed labor have been unable to access obstetric care, but because invading forces from Eritrea, Amhara, as well as the Ethiopian federal government, adopted a deliberate strategy of promoting mass rape as a terrorist weapon against the civilian population. Not only have there been thousands of pregnancies that have resulted from this campaign of rape, but many women were deliberately mutilated by soldiers as part of the terror campaign against the civilian population. Traumatic war-related fistulas have become rather common.

Your wife Helen has been your invaluable companion in your fistula activities. Can you tell us more about Helen, how she has contributed?

Without any doubt, marrying Helen was the best thing that ever happened to me. We have been full partners in all of these humanitarian efforts-as we have in all aspects of life-and although she does not have a medical background (she was a research biochemist) she has been extremely active in these efforts. She ran all of the administrative and financial aspects of our fistula work for years until we found full-time administrative staff, and she has travelled to Africa with me on many different occasions as we tried to put this and other projects together.

When I graduated from medical school, we went to Zaire (now the Democratic Republic of the Congo) to work in a mission hospital for three months. As a newly-minted medical graduate, I was probably more dangerous than helpful, but Helen, who is a world-class seamstress, was incredibly useful. We took hundreds of yards of cloth with us and she spent much of her time sewing up bedsheets, surgical gowns, masks, curtains, whatever was needed to make the hospital run efficiently. I just tried not to kill somebody by making a medical mistake!

In 2015, you returned to your first love, anthropology. You were installed as the inaugural Selina Okin Kim Conner Professor in Arts and Sciences for Medical Anthropology at Washington University in St. Louis. Can you give us more details? What areas of anthropology is your department pursuing?

Washington University has one of the best anthropology departments in the United States, strong in all three of the traditional sub-fields of anthropology: physical (or "biological") anthropology, archaeology, and socio-cultural anthropology. The Department here has strong research interests in all of these areas, particularly medical anthropology

Can you tell us about your lifelong interest in the history and culture of ancient Egypt. Do you have other hobbies and interests?

I became fascinated by ancient Egypt when I was in middle school, and it propelled me to study anthropology and ancient history in college. I actually started graduate work in Egyptology before switching to anthropology and then into medicine, but the antiquity of Egyptian civilization, its history, monuments, written language, and culture are still fascinating to me. In fact, in my retirement, I am pursuing a master's degree in Egyptology from the University of Manchester in

Britain, which concentrates on biomedical aspects of ancient Egypt. I've also been working with a private tutor (herself a PhD in Egyptology) for the last two years to try to master hieroglyphics, and we have almost finished reading and translating the Edwin Smith Surgical Papyrus, the most famous medical treatise from ancient Egypt. The Smith Papyrus is a treatise on trauma that is at least 1,000 years older and far superior in its clinical acumen to anything in the ancient Greek Hippocratic corpus. I'm having an enormously good time with this.

You have had a fascinating colourful career, full of life and movement. Above all, you have worked hard to make a difference where it matters. Looking over your medical career what advice can you give for new physicians interested in the urogynecology field? If some wish to follow your footsteps and work with fistula patients, how do they go about it? How do they develop the superior skill and judgment required to be a competent fistula surgeon?

These injuries from prolonged obstructed labor no longer exist in advanced industrialized countries that have developed effective systems of maternal health care, so the only way to become skilled in this field of medicine is to develop good basic skills in gynecologic surgery and then to partner with someone actively working in an area where there are a large number of obstetric fistulas. This means working with an African surgeon in his or her home environment, to be a learner before becoming a surgeon, and to develop local infrastructure and capacity as the first priority, rather than making the project about your own training.

Finally, congratulations on your first grandchild!

Theodore ("Theo") Wright Wall is, without question, the most wonderful person I have met over the course of the last year! We couldn't be happier!

Having
1. Helen Wall at work as a seamstress in Zaire. Living

2. Lewis Wall with patients at the Evangel Hospital Fistula Center in Jos, Nigeria

3. Lewis breaking ground for the Danja Fistula Center

4. Helen and Lewis Wall at the dedication of the Danja Fistula Center in Niger

5. Lewis and Helen with Dr. Catherine Hamlin in Addis Ababa, Ethiopia, on her 90th birthday

INSTRUCTIONS TO AUTHORS

Pelviperineology is a quarterly published, international, double-blind peer reviewed journal dedicated to the study and education of the pelvic floor as one integrated unit. The publication frequency is 3 times a year (April, August, December) in every 4 months. The core aim of Pelviperineology is to provide a central focus for every discipline concerned with the function of the bladder, vagina, anorectum, their ligaments, muscles and female cosmetic surgery.

Pelviperineology publishes original papers on clinical and experimental topics concerning the pelvic floor diseases in the fields of Urology, Gynaecology and Colo-Rectal Surgery from a multidisciplinary perspective. In the published articles, the condition is observed that they are of the highest ethical and scientific standards and not have commercial concerns. Studies submitted for publication are accepted on the condition that they are original, not in the process of evaluation in another journal, and have not been published before. All submitted manuscripts must adhere strictly to the following Instructions for Authors.

MANUSCRIPT SUBMISSION

Manuscript and illustrations must be submitted via Manuscript Manager. This enables rapid and effective peer review. Contributions will be acknowledged automatically by the Editors. Full upload instructions and support are available online from the submission site. Please read the Authors Instructions carefully before sending your contribution.

Cover Letter: The author, in this letter, should imply a short explanation of their research or writing, the type of the study (random, double-blind, controlled, etc.), the category it is sent for, and whether it has been presented in a scientific meeting or not, in details. Additionally, the address, phone, fax numbers, and e-mail address of the person for contact about the writing should be present at the lower pole of the letter.

The **ORCID** (Open Researcher and Contributor ID) number of the correspondence author should be provided while sending the manuscript. A free registration can create at http://orcid.org.

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Editorial Line: The journal welcomes articles that may update non-specialists in this field, such as internal medicine physicians, family doctors, neurologists, etc., about conditions of general interest involving the pelvic floor and being resolved thanks to a multidisciplinary approach. The ideal article for Pelviperineology should be clear. Its sections should describe precisely the methodology of the study and the statistical methods; illustrations must be of good quality. In highly specialized topics, an easily understandable abstract, a good introduction, and a correct sections distribution are particularly appreciated.

Pelviperineology, despite being an open access journal, does not ask for any financial contribution to the Authors of articles accepted for publication. Pelviperineology is almost entirely funded by sponsors and advertisers that do not affect the Editorial choices and the published content. Advertising is fully and clearly separated from the articles. Material accepted for publication is copy-edited and typeset. Proofs are then sent to contributors for a final check, but extensive changes to the proofs may be charged to the contributors.
For each submission, at least 2 reviewer
suggestions are required on the online article system.

EDITORIAL BOARD
The Editorial Board guides the journal. The updated list of the editorial board members can be reached at Pelviperineology Editorial board page. **Prof. Ahmet Akın Sivaslıoğlu** is the Editor in Chief of Pelviperineology.

PUBLICATION POLICY
Submission is considered on the condition that papers are previously unpublished, are not offered simultaneously elsewhere, that all Authors (defined below) have read and approved the content, that Authors have declared all competing interests, and the work has been conducted under internationally accepted ethical standards after relevant ethical review. Whenever these are relevant to the content being considered or published, the Editors and Editorial board declare their interests and affiliations.

ETHICS
Manuscripts concerned with human studies must contain statements indicating that informed, written consent has been obtained, that studies have been performed according to the *World Medical Association Declaration of Helsinki* and that a local ethics committee has approved the procedures. If individuals might be identified from a publication (e.g. from images), Authors must obtain explicit consent from the individual. Authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed when reporting experiments on animals. A signed statement of informed consent to publish (in print and online) patient descriptions, photographs, video, and pedigrees should be obtained from all persons (parents or legal guardians for minors) who can be identified in such written descriptions, photographs, or pedigrees and should be indicated in the Acknowledgment section of the manuscript. Such persons should be shown the manuscript before its submission. If identifying characteristics are altered to protect anonymity, such as in genetic pedigrees, authors should provide assurance that alterations do not distort scientific meaning, and Editors should note it.

DISCLOSURES
All Authors are responsible for the scientific quality, accuracy, and ethics of the work. Authors are required to disclose interests that might appear to affect their ability to present or review data objectively. These include (but are not limited to) relevant financial (for example, patent ownership, stock ownership, consultancies, speaker's fees), personal, political, intellectual, or religious interests. Authors should describe the study sponsor's role, if any, in study design, collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication. If the supporting source had no such involvement, the authors should state it. Biases potentially introduced when sponsors are directly involved in research are analogous to methodological biases. All Authors must provide details of any other potential competing interests of a personal nature that readers or Editors might consider relevant to their publication. Pelviperineology takes no responsibility for the Authors' statements. The manuscripts, once accepted, become the property of the journal and cannot be published elsewhere without the written permission of the journal.

AUTHORSHIP
As stated in the Uniform Requirements, credit for Authorship requires substantial contributions to

- the conception and design or analysis and interpretation of the data,
- the drafting of the article or critical revision for important intellectual content, and
- final approval of the version to be published.

Anychangeinauthorshipaftersubmissionmustbeapprovedinwritingbyall Authors.

ASSURANCES
In appropriate places in the manuscript, please provide the following items:

- If applicable, a statement that the research protocol was approved by the relevant institutional review boards or ethics committees and that all human participants gave written informed consent.
- The identity of those who analyzed the data.
- For clinical trials, the registration number and registry name.

PEER REVIEW PROCESS IN BRIEF
Submitted manuscripts are subjected to double-blind peer-review. The manuscript submission and Editorial review process are as follows:

An Author submits a manuscript. The manuscript is assigned to an Editor. The Editor reviews the manuscript and makes an initial decision based on manuscript quality and Editorial priorities, usually either to send the manuscript to Peer Reviewers or to reject the manuscript so that the author can submit it to another

journal. For those manuscripts sent to Peer Reviewers, the Editor decides based on Editorial priorities, manuscript quality, reviewer recommendations, and perhaps discussion with fellow Editors. At this point, the decision is usually to request a revised manuscript, reject the manuscript, or provisionally accept the manuscript. The decision letter is sent to the author. Only manuscripts that strictly adhere to Instructions for Authors will be evaluated. Contributions are accepted on the basis of their importance, originality, validity and methodology. Comments of Peer Reviewers may be forwarded to the Author(s) in cases where this is considered useful. The Author(s) will be informed whether their contribution has been accepted, refused, or if it has been returned for revision and further review. The Editor reviews all manuscripts prior to publication to ensure that the best readability and brevity have been achieved without distortion of the original meaning. The Editors reserve the right to reject an article without review.

Statistical Editing: All retrospective, prospective and experimental study articles should be evaluated biostatistically and should include appropriate planning, analysis and reporting. The p value should be clearly stated in the text (eg p=0.014). Statistical Editor reviews only pertinent manuscripts considered for publication. If both the study design and data presented are considered statistically acceptable, the statistical reviewer may suggest acceptance of the manuscript to the responsible Editor. Any methodological and statistical issue detected during the statistical review is addressed to the Authors for clarification. The final acceptance of the paper is contingent on the clarifications made by the Authors according to the statistical reviewer's suggestions.

Language: The official language of the journal is English. All spelling and grammatical errors in submitted articles are corrected by the editor without changing the submitted data. Writing text for spelling and grammar rules is the responsibility of the authors.

Copyright Transfer: In order to notify the copyright transfer, the authors must fill in the copyright transfer form in accordance with the instructions on the relevant page. No fee is paid to the authors for the articles.

Plagiarism: All manuscripts submitted to the journal are screened for plagiarism using the 'iThenticate' software. Results indicating plagiarism may result in manuscripts being returned or rejected. This journal does not accept articles that indicate a similarity rate of more than 15%, according to iThenticate reports.

ARTICLE TYPES

Review Articles: Extent investigation writings including the latest national and worldwide literature about pelvic floor diseases. The review article should be qualified to shed light on a new or controversial area. The journal editor may request the author or authors for review writing. At most include 6000 words, 10 tables and 30 references should be included.

Original Articles: Original articles report the results of fundamental and clinical studies or clinical trials. References and summary are required (see writing preparation section). At most 4000 words, 6 tables and/or figures, additionally abstract and references. Ethics committee approval should be mentioned in the study.

Case Reports: The journal publishes case reports of significant importance in the pelvic floor diseases. For the manuscripts sent to this part, we are looking for the clinical cases that are infrequently reported in scientific previously, unreported clinical reflections or complications of a well-known disease, unknown adverse reactions of known treatments, or case reports including scientific messages that might trigger further new research, preferably. Case reports should be consist of five sections: an abstract, an introduction with a literature review, a description of the case report, a discussion that includes a detailed explanation of the literature review, and a brief summary of the case and a conclusion. It should include at most 2000 words (8 double-spaced pages), 15 or fewer references, and three tables or pictures.

Letter to the Editor: These are the articles that include opinions and solution advice about the pelvic floor, and comments about the articles published in the Pelviperineology or other journals. At most 1500 words (6 double-spaced pages), additionally, references should be included.

Preparation of **review articles, systematic reviews, case reports, and original articles** must comply with study design guidelines:

CHECKLISTS

The presentation of the article types must be designed in accordance with trial reporting guidelines:

Human research: Helsinki Declaration as revised in 2013

Systematic reviews and meta-analyses: PRISMA guidelines

Case reports: the CARE case report guidelines

Clinical trials: CONSORT

Animal studies: ARRIVE and Guide for the Care and Use of Laboratory Animals

PREPARATION OF THE MANUSCRIPT

Text, illustrations, tables etc. must be submitted via Manuscript Manager. Please read Instructions To Authors carefully before sending your contribution.

Text: Please ensure that you have removed any reviewing notes from your manuscripts. The manuscript should be entered or pasted in the Manuscript Manager.

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- **ABSTRACT**
  Structured summary
- **INTRODUCTION**
  Rationale
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- **MATERIALS AND METHODS**

1. Protocol and registration
2. Eligibility criteria
3. Information sources
4. Search
5. Study selection
6. Data collection process
7. Data items
8. Risk of bias in individual studies
9. Summary measures
10. Synthesis of results
11. Section/topic
12. Risk of bias across studies
13. Additional analyses

- **RESULTS**

1. Study selection
2. Study characteristics
3. Risk of bias within studies
4. Results of individual studies
5. Synthesis of results
6. Risk of bias across studies
7. Additional analysis

- **DISCUSSION**

1. Summary of evidence
2. Limitations

- **CONCLUSION**

- **DISCLOSURES**

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* Materials and Methods: One or two sentences reporting the methods;

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ORIGINAL ARTICLE

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Mid-term patient QoL after tot surgery for mixed type urinary incontinence

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ABSTRACT

Objectives: The objective of this study is to determine patients' satisfaction and quality of life after trans-obturator tape surgery in the setting of mixed urinary incontinence with stress urinary incontinence dominance.

Materials and Methods: The patients who had undergone surgery of trans-obturator tape within last 5 years in our clinic were included. All patients had urodynamic evaluations preoperatively. We used incontinence impact questionnare-7 and urogenital distress inventory-6 questionnary forms. Patients were only asked for one-word comment on their satisfaction with the operation: "Satisfied" or "unsatisfied". Also we used visual analog scale 0 to 10 for their satisfaction (happy or unhappy) for trans-obturator tape operation.

Results: Thirty-three women included in our study. Median follow-up was 35 months. 6% of them had early postvoiding residual volume of 50 to 100 mL. None reported to have stress urinary incontinence as preoperatively during follow-up. 60% of them were happy/satisfied for having trans-obturator tape operation. This group's median visual analog scale score was 10.40% of them were unhappy/unsatisfied for having trans-obturator tape operation. This group's median visual analog scale score was one.

Conclusion: Unsatisfied rate is high for trans-obturator tape performed for stress dominant mixed urinary incontinence, though successful surgery. This might be unmet preoperative over-expectations of patients like being dry with surgery for all components mixed urinary incontinence or failure of surgeons to inform well about the surgical outcomes.

Keywords: Incontinence impact questionnare-7 (IIQ-7); mixed urinary incontinence; trans-obturator tape; urogenital distress inventory-6 (UDI-6); visual analogue scale (VAS)

INTRODUCTION

Involuntary leakage of urine is defined as urinary incontinence by the International Continence Society. There are three types of urinary incontinence in particularly. These are stress urinary incontinence (SUI), urge urinary incontinence (UUI) and mixed urinary incontinence (MUI).[1] Urinary incontinence affects quality of life (QoL) negatively. People with urinary incontinence have

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problems in performing their daily activities and in social life. MUI is the complaint of urinary incontinence that contains both urge and stress incontinence. About one-third of women with incontinence have mixed incontinence.[2,3] Behavioral and lifestyle changes such as low caffeine intake, exercise, weight loss, and pelvic floor exercise are accepted as the first-line treatment for MUI.

It is unclear whether surgery or medical treatment is more effective for MUI. While medical treatment is more effective in the urge component of mixed incontinence, surgical treatment is more effective in the stress component. Medical treatment includes anticholinergic drugs. Surgical procedures include tension-free vaginal tape (TVT), the Burch colposuspension, transobturator tape (TOT) treatment. In 2001, the trans-obturator sling application began to be used in humans.[4]

In our study, we aimed to determine the patients' satisfaction and QoL after TOT surgery for mixed type urinary incontinence patients in the mid-term follow-up period.

MATERIALS AND METHODS

Patients who underwent TOT due to MUI in our clinic in the last 5 years were retrospectively screened. Patients who could not be reached for the questionnaires were excluded from the study. The patients' demographics and medical histories were noted. Medical history includes preoperative anticholinergic use, chronic diseases, previous operations, preoperative cystoscopy findings, number and type of delivery, preoperative overactive bladder findings and postoperative complications. All patients underwent preoperative urodynamics to exclude neurological diseases.

All patients had undergone cystoscopy to confirm MUI and decided on surgery. In order to decide on surgery, stress test positivity, Marshall Marchetti test positivity and whether the Q-tip test was greater than 30 degrees were checked in cystoscopy and urogynecological examination. An informed consent form was obtained from each patient before operation. We used questionnaires of urogenital distress inventory-6 (UDI-6) and incontinence impact questionnaire-7 (IIQ-7) to evaluate patients' QoL after TOT in the mid-term follow-up period. Total UDI-6 scores ranged between 0-18 points and IIQ-7 scores ranged between 0-21 points. Higher scores are associated with poorer QoL. We also questioned whether they were happy with the operation and their satisfaction level using a visual analog scale (VAS) of 0 to 10. The patients' QOL and satisfaction score were determined and analyzed to find any clinical correlations of scores with clinical parameters. There were 46 patients operated with TOT at beginning. Thirty-three patients were asked to fill out UDI-6, IIQ-7 and VAS.

Statistical Analysis

The continuous variables were expressed as medians, counts and percentages where appropriate. The data were recorded in excel sheets (Office Professional Plus 2016, Microsoft) and analyzed using statistical software (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.). Continuous variables including age, body mass index (BMI) and questionnaires' scores were compared with Mann-Whitney U test. A p-value <0.05 was considered statistically significant.

RESULTS

Thirty-three women were included in the study with a median age of 55 years. Their median follow-up period was 35 months. 73% had one or more co-morbid diseases. 46% of them were smokers. 39% of them had previous pelvic surgery related to gynecology. 88% of them were on antimuscarinic medication for urge incontinence. 9% was nullipara. Median numbers of live births were 3 with birth related complications in 42% of them. Preoperative median bladder capacity was 400 mL. 6% of them had early operation failure and 6% had early postoperative postvoiding residual volume of 50 to 100 mL. None had urinary retention. None reported to have SUI as preoperatively. 60% of the patients reported themselves as happy/satisfied for having been operated with median VAS of 10 whereas other 40% reported as unhappy/unsatisfied with a VAS score of 1. Surgery satisfied group were insignificantly older, and had a lower BMI, which are statistically insignificant (Table 1). The median UDI-6 scores were significantly lower in satisfied group compared to unsatisfied (0 vs. 15.5) (p≤0.001) and IIQ-7 scores were significantly lower in satisfied group compared to unsatisfied (3 vs. 11) (p≤0.001). No other clinical variable was distinct between two groups.

DISCUSSION

Urinary incontinence is an important health problem that affects QoL. To perform surgery, the diagnosis of SUI dominant MUI must be confirmed by cystoscopy. It is necessary to accurately determine the stress component weight in MUI. Because we thought that patients with SUI dominant MUI would more benefit from surgery.

Table 1. UDI-6, IIQ-7 scores of the patients

	Satisfied	Unsatisfied	p-value
Age (years)	57	52	0.511*
BMI (kg/m^2)	31	33.3	0.108*
IIQ-7 score	0	15.5	<0.001*
UDI-6 score	3	11	<0.001*

*Mann-Whitney U test, BMI: body mass index; IIQ-7: incontinence impact questionnare-7; UDI-6: urogenital distress inventory-6

In all patients in the study, the complaint of stress incontinence component after surgery improved compared to the preoperative period. Similarly, lower UDI-6 and IIQ-7 scores were observed in patients with low VAS scores and who were satisfied with the operation. In the current study, satisfaction and QoL of patients after TOT were determined by subjective evaluation of patients through questionnaires.

There were the most significant improvements at urgency and UUI after TOT in the literature. In a review there was 30 to 85% improvement in urgency and UUI after MUS during a follow-up of 3 to 60 months.[5] There are studies showing that middle urethral sling surgery also improves storage symptoms in MUI. Verified questionnaires evaluating stress and compression components can be an indicator for surgical success when administered preoperatively.[6] It becomes difficult to analyze the results of urinary incontinence surgery because there are no superior questionnaires that can evaluate the success of urinary incontinence surgery universally.[7]

The UDI-6 questionnaire form contains high quality evidence and IIQ-7 questionnaire form contains moderate quality evidence in a systematic review.[8]

In a study in which unoperated stress and mixed type incontinence patients and urge type incontinence patients were examined in terms of physical, emotional and social QoL; the lowest score was observed in mixed type incontinence patients.[9] This shows us that these patients may have an improvement in their QoL after surgery with a high probability.

In the study where the International consultation incontinence questionnaire short-form was used, it was seen that the QoL of MUI patients was more affected.[10] This form contains questions about the frequency of urinary incontinence,the amount of urinary incontinence, how much it affects daily life, and in which cases it causes urinary incontinence.

In a survey study in which MUI patients were questioned using UDI-6, the King's Health Questionnaire and Patient Global Impression of Improvement questionnaires, it was shown that surgical success was less in patients over the age of 60 and in menopausal patients.[11]

In a review, it was observed that mixed incontinence patients had lower satisfaction after midurethral sling surgery than stress incontinence patients.[12]

In a study in which the QoL of patients with SUI and MUI was investigated using the UDI-6 questionnaires, a more clinically significant improvement in postoperative UDI-6 score was observed in patients with MUI.[13] In this study, both SUI and MUI patients underwent retropubic midurethral sling and simultaneous prolapse repair. In contrast to our study, patients with MUI and SUI were compared.

In a study that included patients who underwent surgical treatment for mixed or urge type incontinence, 2/3 of patients underwent TOT for persistent post-operative stress incontinence.[14] The surgical methods in this study were "cervical-rectal-sacral fixation" and "vaginal-rectal-sacral fixation". Additional alternative treatments may be required for patients with mixed incontinence who underwent TOT/TVT but did not improve in the urge component after treatment.[15]

Although people with neurological diseases were excluded in our study, in a study comparing the results of mid-uretral sling surgery, no significant difference was found in terms of improvement in the urge component with and without neurological disease.[16]

In a randomized clinical study comparing MUI patients who underwent surgery only and combined behavioral and pelvic floor muscle therapy in addition to surgery; a non-significant difference in incontinence symptoms was detected at 12-month follow-up. But this difference did not meet the prespecified threshold for clinical importance.[17]

In a study of persistence of urgency and UUI in women with mixed urinary symptoms after midurethral slings, the overall satisfaction score was lower in patients who continued to feel urge after midurethral sling surgery or who continued to have UUI.[18] When these patients were asked if they recommended surgery to their friends, they received a negative response.

In a study that searching about treatments of MUI, it is emphasized that the evaluation of mixed incontinence should be carried out carefully and comprehensively. Because conditions such as preoperative detrusor hyperactivity, urge component dominance affect surgical success.[19]

Mid-urethral sling surgery is recommended in patients with MUI for whom behavioral therapy is not effective. It is difficult to predict which patient will benefit from surgery exactly among these patients. For this reason, it is important from the point of view of the clinical approach to classify MUI into subtypes by conducting further research.[20]

In our study, the high preoperative urge component showed that the dissatisfaction rate was high in the follow-up after surgery.

CONCLUSION

The limitations of our study were that there were only thirty-three women and that it was a retrospective study. It was observed that TOT operation significantly improved the stress components of the patients in general. According to the results

of the questionnaires directed to the patients, it was observed that the stress incontinence components of the patients were greatly improved after TOT.

It was seen that the factors of BMI, patient age, chronic diseases and birth history did not create statistically significant differences between the two groups (satisfied/non-satisfied). A study with more patients is necessary for us to make a more accurate assessment.

ETHICS

Ethics Committee Approval: University of Health Sciences Türkiye, İstanbul Health Practice & Research Center, Ethics' Committee approval was taken (no: 75, date: 25.02.20)

Informed Consent: Informed consent form was obtained.

Peer-review: Internally and externally peer-reviewed.

Contributions

Surgical and Medical Practices: H.K., E.A., M.H.E.A.; Concept: H.K., E.A., M.H.E.A.; Design: H.K., E.A., M.H.E.A.; Data Collection or Processing: H.K., E.A., M.H.E.A.; Analysis or Interpretation: H.K., E.A., M.H.E.A.; Literature Search: H.K., E.A., M.H.E.A.; Writing: H.K., E.A., M.H.E.A.

DISCLOSURES

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Adelmidrol + hyaluronic acid in the treatment of symptoms associated with intravesical anticancer therapy in non-muscle invasive bladder cancer. An observational retrospective investigation

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ABSTRACT

Objectives: Intravesical therapy with Bacillus Calmette-Guérin and chemotherapy are an integral part in the management of non-muscle invasive bladder cancer (NMIBC), which is administered after transurethral surgical resection (TUR) of tumour to prevent relapse and progression of the disease. However, these therapies frequently cause side effects such as cystitis-like symptoms, which often can lead to treatment discontinuation. The purpose of this investigation was to evaluate the effect of intravesical administration of adelmidrol (AD) and hyaluronic acid (HA) on the typical symptoms in patients undergoing intravesical anticancer treatment for NMIBC, after TUR.

Materials and Methods: Thirty-one patients, who underwent TUR for NMIBC and had completed a cycle of intravesical anticancer treatment associated with AD + HA instillations, were considered for this retrospective investigation. For all patients, the main collected outcomes were: Pain intensity, urgency and discomfort related to frequent micturition (FM-related discomfort) evaluated by visual analogue scale, symptoms frequency and patient's degree of concern evaluated by pelvic pain and urgency/frequency patient symptom scale, and health-related quality of life detected with the 12-item short form survey.

Results: Intravesical instillation of AD + HA as an add-on treatment to intravesical anticancer therapy allowed to keep under control pain intensity, urgency and FM-related discomfort, enabling all patients to complete the entire course of anticancer treatment.

Conclusion: This retrospective investigation shows the potential efficacy of AD + HA to control anticancer treatment-related side effects. Larger randomized controlled studies are needed to confirm these encouraging results.

Keywords: Adelmidrol; chemotherapy; cystitis; hyaluronic acid; intravesical therapy; non-muscle invasive bladder cancer

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INTRODUCTION

Intravesical therapy is an integral part in the management of non-muscle invasive bladder cancer (NMIBC), which is administered after transurethral surgical resection (TUR) of tumours, to prevent relapse and progression of the disease. Immunotherapy with Bacillus Calmette-Guérin (BCG) and chemotherapy with mitomycin C (MMC) or epirubicin (EPI), are the most used intravesical therapies.[1,2] BCG is typically used for cancers with an intermediate or high risk of progression, while intravesical chemotherapy is usually adopted for cancers with a high risk of recurrence, but a low risk of progression.[3-5] Both intravesical chemotherapy and BCG can lead to side effects of different degrees. The most frequent are cystitis-like symptoms such as urgency, dysuria, and increased micturition frequency. Often, these local side effects can lead to treatment discontinuation or incomplete treatment, resulting in suboptimal outcomes. Therefore, prevention and management of side effects are paramount to ensure oncologic treatment efficacy.[1,3]

The complex symptomatology provoked by intravesical therapy with BCG, MMC or EPI chemotherapy, is the consequence of inflammatory processes. Particularly intense and/or persistent traumatic, chemical, hormonal, infectious, and iatrogenic stimuli, led to the progressive impairment of the urothelial structure due to mast cells (MCs) activation.[6] Activated MCs can directly interact with other cells of the immune system and guide the inflammatory reaction promoting vascular permeability, local tissue response and the recruitment of various inflammatory mediators.[7] Inappropriate and persistent MCs stimulation can transform the local and acute inflammatory response into a chronic and systemic inflammatory disease, with amplification of painful stimuli too.[8,9] Therefore, an approach based on MCs modulation could be effective in counteracting intravesical therapy-related side effects.

With this aim, adelmidrol (AD), a derivative of azelaic acid, could represent a possible therapeutic strategy. AD is in fact able to keep MCs normal reactivity, through its capacity to increase the endogenous levels of the natural MCs modulator: Palmitoylethanolamide (PEA).[10-14] The beneficial effects of AD were already demonstrated in acute and chronic inflammation, as well as in patients with chronic interstitial cystitis/bladder pain syndrome (IC/BPS).[15,16]

The purpose of this investigation was to evaluate the efficacy of intravesical administration of a product containing AD in combination with hyaluronic acid (HA)[17-22], in counteracting antitumor therapy-related side effects.

MATERIALS AND METHODS

This manuscript reports the data collected at the Urology Outpatient Clinic of the Galliera Hospital (Genova, Italy) between October 2019 and November 2021, on the clinical practice adopted in patients starting the 1st cycle of intravesical therapy after TUR of NMIBC.

The approach used was to perform intravesical instillations with a medical device combining AD 2% + HA 0.1% (Vessilen®, Epitech Group SpA) in add-on to antitumor therapy with BCG, EPI or MMC.

AD + HA posology was decided on the base of a previous similar experience reported in literature.[16] Data were collected at the evaluation times normally performed at the urology clinic. Therapeutic scheme and follow-up times are reported in Figure 1.

Ethics committee approval and patients written informed consent were obtained for data publication.

Outcomes collected were: 1) Pain, urgency and discomfort related to frequent micturition (FM-related discomfort) by Visual Analogue Scale (VAS). VAS score ranges from 0 mm to 10 mm, with higher score representing higher symptoms intensity;[23] 2) Frequency of cystitis-like symptoms and patients concern by pelvic pain and urgency/frequency patient symptom (PUF) scale. PUF-Total score is the sum of "PUF-symptom" and "PUF-bother" scores. Total score ranges from 0 to 35, with higher score representing worst condition;[24] 3) Health-related quality of life with 12-item short form (SF-12) survey. SF-12 evaluates both the physical (PCS) and the mental (MCS) components. Total score ranges from 0 to 100, with higher score indicating better health.[25] Intensity of pain, urgency and FM-related discomfort

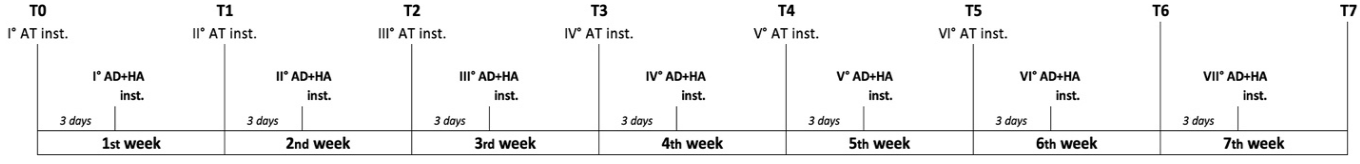


Figure 1. Treatment scheme and evaluation time points
AT: antitumor therapy; inst.: instillation

were evaluated weekly from T0 to T7. PUF and SF-12 were completed by patients before the start (T0) and at the end (T7) of AD + HA treatment.

Beside these evaluations, it was performed a descriptive analysis of the percentage of patients who experienced local side effects over the entire observation period: VAS pain or urgency intensity score ≥5 was considered representative of clinically significant side effects. This value includes intensity between moderate and severe and it was established arbitrarily as a symptom threshold above which the continuation of anticancer therapy could be compromised.[26] As FM-related discomfort was not a symptom but a bother, and therefore very subjective, it was not possible to establish a reliable cut-point for this parameter. Alternatively, the combination between answers to question n°1 "How many times do you go to the bathroom during the day?" and question n°2a "How many times do you go to the bathroom at night?" of the PUF scale was considered for this analysis at T0 and T7 (time points at which the PUF was administered). Voiding frequency was considered normal if both scores of PUF questions n°1 and n°2a were 0-1, while it was considered altered with a score >1 at one and/or both questions.[24]

Statistical Analysis

Statistical analysis was performed using the generalized linear mixed model considering three different time points: the beginning of the anticancer therapy (T0) (3 days before the start of AD + HA therapy), the end of the anticancer therapy (T5), and the last control after the end of AD + HA administration (T7). Post-hoc analyses were performed with the correction of Tukey-Kramer for multiple comparisons. Variables such as gender, age, tumour staging and type of intravesical anticancer therapy were included in the model as covariates. A *p*-value of less than 0.05 was considered significant. All scores are given as mean ± standard error, unless otherwise specified.

RESULTS

Thirty-one patients (13 female and 18 males) with a mean age of 71 years old, treated with AD + HA instillations in add-on to intravesical anticancer therapy after TUR for NMIBC, were considered in this retrospective investigation. Anticancer treatment was performed with intravesical instillations of BCG in 71%, MMC in 10% and EPI in 19% of cases. All demographics and patients baseline characteristics are reported in Table 1.

Pain intensity, urgency and FM-related discomfort significantly decreased over time. Pain intensity decreased from 1.5±0.48 (T0) to 1.4±0.42 (T5) reaching 0.4±0.18 (T7) (T0-T5-T7 p=0.01; T0-T5 n.s.; T5-T7 p=0.01) (Figure 2A). None of the considered covariates had any significant influence on treatment efficacy. Urgency decreased from 3.0±0.66 (T0) to 2.1±0.58 (T5) reaching 1.5±0.44 (T7) (T0-T5-T7 p=0.01; T0-T5 n.s.; T5-T7 n.s.) (Figure 2B). Urgency increased with age (p=0.03). FM-related discomfort decreased from 3.3±0.56 (T0) to 3.0±0.50 (T5) reaching 2.2±0.46 (T7) (T0-T5-T7 p=0.007; T0-T5 n.s.; T5-T7 p=0.007) (Figure 2C). Gender influenced FM-related discomfort, with women having a greater discomfort (p=0.03).

At the end of analgesic treatment (T7) average values of the PUF-total score were indicative of a significative improvement of patients concern (p=0.04). In particular, the PUF-symptoms score showed a significant improvement over time, moving from a mean value of 5.4±0.54 (T0) to 4.4±0.47 (T7) (p=0.01); PUF-bothers score showed a reduction from T0, passing from a value of 2.9±0.05 (T0) to 2.5±0.43 (T7) (n.s.) (Figure 3). None of the covariates significantly affected neither the symptoms nor the bother score.

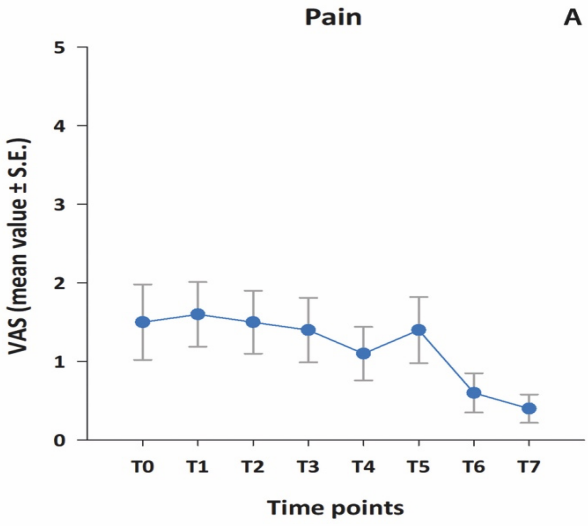
SF-12 PCS changed from 48.7±1.53 (T0) to 50.4±1.45 (T7) (n.s). SF-12 MCS moved from 52.1±1.57 (T0) to 51.0±1.58 (T7) (n.s.).

The percentage of patients who experienced symptoms of pain intensity and/or urgency with VAS ≥5 was 35% (T0), decreased to 23% (T5) and to 13% at the end of AD + HA treatment (T7) (Table 2). In particular, percentage of patients who experienced pain intensity with a VAS score ≥5 was 16% (T0), decreased to 10% (T5) and 3% (T7), while percentage of patients who experience urgency with a VAS score ≥5 was 32% (T0), decreased to 23% (T5) and 13% (T7) (Table 2). Percentage of patients with altered daily voiding frequency (according to questions n°1 and n°2a of the PUF scale) decreased from 77% (T0) to 68% (T7) (Table 3).

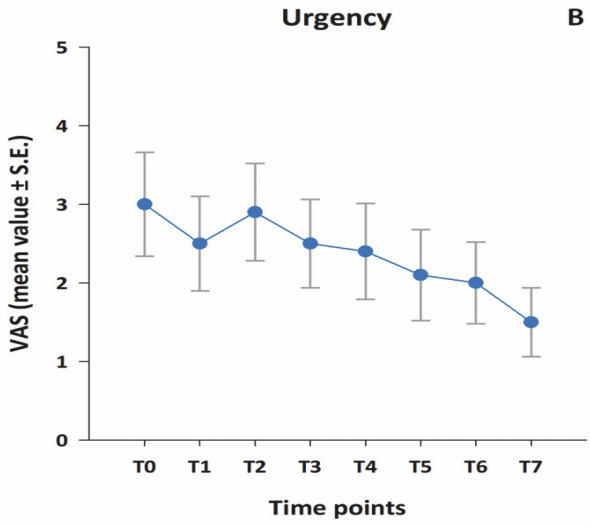
Table 1. Patient demographic data and baseline characteristics

Age (mean ± S.D.)	**71±6**
Gender n (%)	
Male	**18 (58)**
Female	**13 (42)**
Stage of cancer n (%)	
TAHG	**12 (39)**
TALG	**4 (13)**
T1HG	**13 (42)**
T1HG CIS	**2 (6)**
Anticancer therapy n (%)	
BCG	**22 (71)**
MMC	**3 (10)**
EPI	**6 (19)**

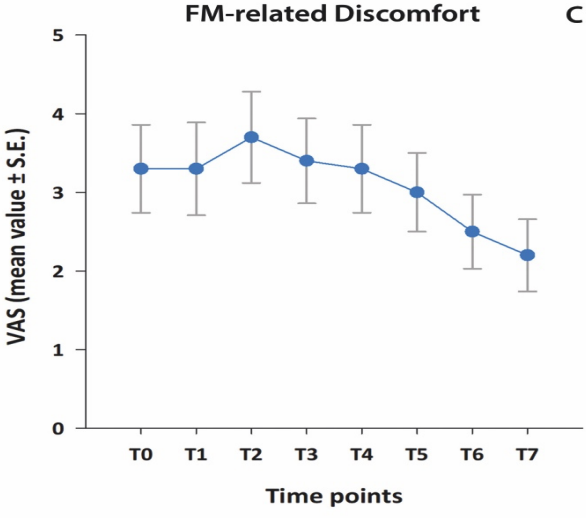
S.D.: standard deviation; BCG: Bacillus Calmette-Guérin; MMC: mitomycin C; EPI: epirubicin



GLMM analysis (time effect)	P-Value
T0-T5-T7	**p=0.01**
Post-hoc analysis	
T0-T5	n.s
T5-T7	**p=0.01**



GLMM analysis (time effect)	P-Value
T0-T5-T7	**p=0.01**
Post-hoc analysis	
T0-T5	n.s
T5-T7	n.s



GLMM analysis (time effect)	P-Value
T0-T5-T7	**p=0.007**
Post-hoc analysis	
T0-T5	n.s
T5-T7	**p=0.007**

Figure 2. Changes over time in pain intensity, urgency and FM-related discomfort evaluated by VAS at the different evaluation time points

Data are expressed as mean ± S.E.

Intensity of pain (A), urgency (B) and FM-related discomfort (C) decreased significantly over time (T0-T5-T7 $p<0.05$). Post-hoc analysis results are shown in the figure

S.E.: standard error; n.s.: not significant

Table 2. Percentage of patients with clinically significant pain intensity and urgency at the different evaluation time points

Symptoms	NRS scores	Percentage of patients							
		T0	T1	T2	T3	T4	T5	T6	T7
		n=31	n=31	n=31	n=31	n=30	n=31	n=31	n=31
Pain intensity	≥5	16%	13%	10%	10%	6%	10%	3%	3%
Urgency	≥5	32%	23%	29%	29%	27%	23%	16%	13%
Pain intensity and/or urgency	≥5	35%	26%	32%	32%	29%	23%	16%	13%

Table 3. Percentage of patients with normal or altered voiding frequency at baseline (T0) and the end of AD + HA treatment (T7)

Daily voiding frequency	Percentage of patients	
	T0	T7
	n=31	n=31
Patients with normal frequency (score 0-1 on both questions 1 and 2a of PUF questionnaire)	23%	32%
Patients with altered frequency (score >1 on question 1 and/or 2a of PUF questionnaire)	77%	68%

PUF: patient symptom; AD: adelmidrol; HA: hyaluronic acid

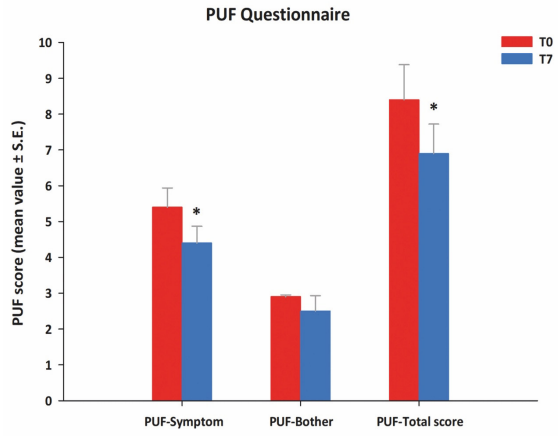


Figure 3. Symptom frequency and patient bother evaluated by PUF scale at baseline (T0) and at the end of AD + HA treatment (T7)
Data are expressed as mean ± S.E.
PUF-total score and PUF-symptom score significantly improved between T0 and T7 ($p<0.05$); PUFbother score showed a slight reduction (n.s.)
**$p<0.05$; S.E.: standard error; n.s.: not significant; PUF: patient symptom*

No patient discontinued treatment prematurely and there was no change in therapeutic scheme established.

DISCUSSION

Intravesical chemotherapy with MMC or EPI and immunotherapy with BCG are adjuvant therapies widely used after TUR to prevent recurrence and progression of bladder cancer.[4,5]

Despite their great efficacy, these therapies have several local side effects such as the onset of urgency, dysuria, and increased micturition frequency, that lead to treatment delay or reduction in 55-83% of cases, and even to its interruption in 30%.[21,27,28] Finding a new strategy to manage these side effects is therefore paramount to ensure oncologic treatment efficacy.[1,3]

AD is a compound able to increase PEA endogenous levels.[10,12,14] Oral administration of PEA in its micronized (m-PEA) and ultramicronized (um-PEA) forms already demonstrated to be effective in increasing intravesical anticancer therapy tolerability and improving pain in patients with BPS, thanks to its ability to modulate MCs degranulation.[29,30] Likewise, instillations of AD together with HA (Vessilen®, Epitech Group Spa), led to a significant improvement of pain, urgency and frequency in patients suffering from chronic IC/BPS or other urothelial dysfunction.[16]

In this retrospective study, AD + HA instillations were introduced from the beginning of the 1st cycle with BCG, MMC/EPI, when the expected frequency of side effects is higher.

Overall, AD + HA allowed to keep under control intensity of pain, urgency and FM-related discomfort, enabling all patients to complete the entire cycle of adjuvant anticancer treatment.

Moreover, the continuation of AD + HA treatment after the end of anticancer cycle, led to a further improvement of symptomatology (reduction of VAS score and percentage of patients with side effects).

In particular, patients with at least one cystitis-like symptom from moderate to severe intensity (VAS score ≥5) were 35% at

T0, reduced to 23% at T5 and to 13% at T7. PUF total score at the end of AD + HA therapy reported a significantly improvement in symptoms and of their impact on patients life ("PUF-symptom" and "PUF-bother" scores respectively). Consistently with these results, no substantial differences were observed in SF-12 questionnaire for either PCS or MCS, from T0 to T7.

All patients completed the therapeutic scheme established and no patient reported side effects related to AD + HA.

In the analysed population, pain, urgency, FM-related discomfort means VAS scores and PUF basal scores were relatively low compared to literature data.[20,22] This occurred because in the statistical analysis it was considered each patient treated with AD + HA, including those with no, or mild side effects. However, it is relevant to point out that many of these patients had no side effects at all, or showed only mild symptoms throughout the entire course of treatment.

Adding AD + HA could seem burdensome, taking account of the already high costs of chemo-immuno-prophylaxis. However, it has to be considered the lack of anticancer therapy discontinuation, together with the reduction of radical cystectomies number, and of further endoscopic bladder surgical treatments need.

Furthermore, despite the increased number of catheterizations, there were no infectious manifestations such as fever or macrohematuria, thus highlighting the absence of negative aspects in adding AD + HA to current clinical practice.

These are very preliminary results, on a small number of patients, lacking of a control group. A prospective, randomized and controlled study is required to optimize treatment protocol and confirm these promising data. It would be furthermore appropriate to evaluate the use of AD + HA during the 2nd cycle of anticancer treatment, a period equally subjected to side effects onset. Follow-up data are not yet available, but their collection is in progress, to confirm the absence of long-term consequences of AD + HA add-on, on the oncologic follow-up.

CONCLUSION

This retrospective observational study supports the introduction into clinical practice of AD + HA for the management of oncologic patients, in order to reduce anticancer treatment-related side effects and allow, as much as possible, the adherence to the established therapeutic protocol.

ACKNOWLEDGMENTS

The authors are grateful to EPITECH Group SpA for the information support, in particular to Francesco Puglisi, Area Manager Liguria.

ETHICS

Ethics Committee Approval: The study was approved by the Ethics Committee of Liguria-Italy (Register no: 399/2022-DB id 12315). The study was conducted in accordance with the principles of Helsinki Declaration.

Informed Consent: Retrospective study. Written informed consent was obtained from each patient.

Peer-review: Externally peer-reviewed.

Contributions

Surgical and Medical Practices: G.C., F.C., C.I.; Concept: G.C.; Design: G.C., S.T.; Data Collection or Processing: S.T., A.L.C.; Analysis or Interpretation: G.C., F.C.; Literature Search: G.C.; Writing: G.C.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL ARTICLE

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Retrospective analysis of urogynecological symptoms of patients undergoing gynecological oncology surgery

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ABSTRACT

Objectives: Treating gynecological cancer with radical surgery, pelvic radiotherapy, and systemic chemotherapy may lead to pelvic floor dysfunction.

Materials and Methods: Lower urinary tract symptoms are common after surgery for gynecological cancer. We used the Urogenital Distress Inventory (UDI)-6, Incontinence Impact Questionnaire (IIQ)-7, and International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) to compare the severity of urinary incontinence and quality of life between patients who underwent staging surgery for gynecological caner and those who underwent hysterectomy for benign disease. In total, 50 patients with cancer and 50 patients with benign disease were included in the patient and control groups, respectively.

Results: There were no significant differences between the groups in terms of preoperative IIQ-7, UDI-6, and ICIQ-SF scores. There was a significant difference between the groups in scores 1 and 12 months after surgery. Postoperative IIQ-7, UDI-6, and ICIQ-SF scores were significantly increased compared to preoperative scores, although there were no significant differences between preoperative and postoperative scores in the control group. Incontinence was present after surgery in 15 (43.2%) and 4 (21.1%) patients in the test and control groups, respectively. In multivariate analyses of variance, surgery for cancer was an independent risk factor for urinary incontinence.

Conclusion: Genitourinary symptoms should be evaluated in cancer patients undergoing staging procedure. The quality of life of patients should be assessed in terms of incontinence in the postoperative period.

Keywords: Hysterectomy; quality of life; urinary incontinence

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INTRODUCTION

After breast cancer, gynecological cancers are a leading cause of morbidity and mortality in women. The treatment of gynecological cancers includes radical surgery, pelvic radiotherapy, and systemic chemotherapy, which may lead to pelvic floor dysfunction.[1] Lower urinary tract symptoms are common after surgery for gynecological cancer, with a frequency of 12.2-51%.[2] These symptoms significantly affect the quality of life of patients.

Urinary incontinence (UI), which is characterized by objective, unintentional loss of urinary control, makes it difficult to maintain hygiene and leads to social, emotional, sexual, and economic problems.[3] It is affected by multiple factors and leads to an impaired quality of life for patients. An understanding of UI and its risk factors is essential to preventing and treating UI. The role of surgery in the treatment of urinary dysfunction is not clear. Multiple mechanisms may be involved in bladder dysfunction, including impaired blood flow to the nerve fibers of the pelvis plexus during bladder dissection.[4] In patients with gynecological cancers, the supporting tissues of the cervix, such as the vesicouterine and cervicouterine ligaments, are separated from the cervix by the removal of the uterus.[5] Relaxation of the pubococcygeus muscle and inadequate urethral closure lead to the development or exacerbation of stress incontinence.[6] In cases of damage to the hypogastric nerve (sympathetic system) during hysterectomy, the pelvic nerve (parasympathetic system) dominates and leads to urinary trapping and urgency.[7]

In this study, we used scores on the Urogenital Distress Inventory (UDI)-6, Incontinence Impact Questionnaire (IIQ)-7, and International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) to confront the severity of UI and quality of life between patients who underwent stating procedure for gynecological cancer and those who underwent hysterectomy for benign disease.

MATERIALS AND METHODS

This trial was conducted between January 1, 2016, and December 31, 2021, at the Gynecological Oncology Clinic Muğla Sıtkı Koçman University. We enrolled patients who underwent staging surgery (total hysterectomy, bilateral salpinoophorectomy, and pelvic and paraaortic lymphadenectomy with or without infracolic omentecomy) for endometrial or ovarian cancer by laparoscopy or laparotomy and those who underwent total hysterectomy and bilateral salpingoophorectomy for benign disease. Patients diagnosed with incontinence after anamnesis and physical examination were excluded. The UDI-6, IIQ-7, and ICIQ-SF were administered 1 week before surgery to patients and during routine clinical visits to controls.

We excluded patients who did not complete the questionnaires or were lost to follow-up, who had mental disorders, who were unable to communicate, who experienced incontinence due to other causes (e.g., neurogenic bladder, psychogenic incontinence, drug use), who had a history of urogynecological surgery, and who underwent urogenital procedures or experienced intraoperative complications.

Preoperative examination findings and questionnaire scores were recorded. The questionnaires were administered face to face to patients who presented for follow-up, and patient confidentiality was maintained. Age at the time of operation; gravidity and parity; body mass index; previous surgeries; comorbidities; drug use; smoking; alcohol consumption; and preoperative, 1-month postoperative, and 12-month postoperative UDI-6, IIQ-7, and ICIQ-SF scores were recorded.

The validated Turkish transcription of the aforementioned questionnaires were used. The severity, frequency, type, and influence on quality of life of UI were evaluated with the ICIQ-SF. The UDI-6 was used to appraise the type and impact on quality of life of UI. The IIQ-7 was utilized to assess the psychosocial effects of UI. Maximum scores on the ICIQ-SF, UDI-6, and IIQ-7 are 24, 18, and 21, respectively. Increasing scores indicate worse quality of life and symptoms.

Statistical Analysis

An SPSS (version 18.0; IBM, Armonk, NY, USA) was employed for statistical analyses. Descriptive analyses of the data are presented in the tables. The Shapiro-Wilk test was employed to evaluate the normality of the data distribution. Parametric and non-parametric tests were used to evaluate normally and non-normally distributed variables, respectively. Independent-samples Student's t-test, Mann-Whitney U test, and chi-squared test (Pearson chi-squared and Monte-Carlo chi-squared) were used to compare independent groups. $P<0.05$ was taken to indicate statistical significance.

RESULTS

This study included 50 patients with cancer (test group) and 50 patients with benign disease (control group). Demographic data were similar in the two groups (Table 1). The most common surgical indications in the test and control groups were endometrial cancer and fibroids, respectively.

None of the study patients had intraoperative or postoperative complications. Table 2 presents the adjuvant treatments used in this trial. No significant differences between the groups in terms of preoperative IIQ-7, UDI-6, or ICIQ-SF scores were found (Table 3). However, there were significant differences in the

questionnaire scores between the groups 1 and 12 months after surgery.

Although IIQ-7, UDI-6, and ICIQ-SF scores increased significantly after surgery in the test group, there were no significant differences between preoperative and postoperative scores in the control group (Table 4). UI incontinence developed in 15 (43.2%) and 4 (21.1%) patients in the test and control groups, respectively (Table 5). In multivariate analyses of variance, surgery due to cancer was an independent risk factor for UI (hazard ratio: 5.35, 95% confidence interval: 1.2-23.5, p=0.02; Table 6).

Table 1. Demographic characteristics of the study participants

Variable	Test group (n=50)	Control group (n=50)	*p*-value
Age	54.1±11.1	53.8±10.05	0.91
Number of deliveries	2.34±1.06	2.28±1.32	0.86
Indication			<0.001
Endometrial cancer	34 (68.0%)	-	
Ovarian cancer	16 (32.0%)	-	
Fibroids	-	14 (28.0%)	
EIN	-	13 (26.0%)	
CIN	-	8 (16.0%)	
AUB	-	15 (30.0%)	
Type of delivery	47	45	0.91
Vaginal	38 (80.9%)	36 (80.0%)	
Cesarean	9 (19.1%)	9 (20.0%)	
BMI	27.4±3.6	27.9±4.24	0.33
BMI			0.41
<30	36 (72.0%)	33 (66.0%)	
≥30	14 (28.0%)	17 (34.0%)	
Menopause			0.41
Postmenopausal	32 (64.0%)	34 (68.0%)	
Premenopausal	18 (36.0%)	16 (32.0%)	
Sexually active			0.38
Yes	43 (86.0%)	45 (88.0%)	
No	7 (14.0%)	5 (12.0%)	
Smoking			0.30
Yes	39 (78.0%)	42 (84.0%)	
No	11 (22.0%)	8 (16.0%)	
Alcohol			0.50
Yes	47 (94.0%)	46 (92.0%)	
No	3 (6.0%)	4 (8.0%)	
Diabetes mellitus			0.79
Yes	41 (82.0%)	42 (84.0%)	
No	9 (18.0%)	8 (16.0%)	
Hypertension			0.46
Yes	41 (82.0%)	38 (76.0%)	
No	9 (18.0%)	12 (24.0%)	
Surgery type			<0.001
Laparoscopy	20 (40.0%)	44 (88.0%)	
Laparotomy	30 (60.0%)	6 (12.0%)	

BMI: body mass index; EIN: endometrial intraepithelial neoplasia; CIN: cervical intraepithelial neoplasia; AUB: abnormal uterine bleeding

DISCUSSION

This case-control trial included patients who underwent staging surgery by laparoscopy or laparotomy for endometrial or ovarian cancer and those who underwent total hysterectomy and bilateral salpinoophorectomy for benign disease. We evaluated the short- and long-term risk of developing UI, its effects on quality of life, and its association with previous surgeries

Table 2. Comparison of the endometrial and ovarian cancer groups in terms of cancer stage, brachytherapy, radiotherapy + brachytherapy, radiotherapy + chemotherapy, chemotherapy, omentectomy, pelvic lymph node dissection, and paraaortic lymph node dissection

	Endometrial cancer	Ovarian cancer	*p*-value
Stage			0.001
1	25 (78.1%)	7 (21.9%)	
2	6 (100.0%)	0 (0.0%)	
3	3 (25.0%)	9 (75.0%)	
Brachytherapy			0.005
Yes	12 (35.3%)	0 (0.0%)	
No	22 (64.7%)	16 (100.0%)	
Radiotherapy + brachytherapy			0.03
Yes	8 (23.5%)	0 (0.0%)	
No	26 (76.5%)	16 (100.0%)	
Radiotherapy + chemotherapy			0.45
Yes	2 (5.9%)	0 (0.0%)	
No	32 (94.1%)	16 (100.0%)	
Chemotherapy			<0.001
Yes	1 (2.9%)	13 (81.3%)	
No	33 (97.1%)	3 (18.8%)	
Omentectomy			0.60
Yes	23 (67.6%)	11 (68.8%)	
No	11 (32.4%)	5 (31.3%)	
Pelvic lymph node dissection			
	24.7±11.8	25.68±8.92	0.78
Paraaortic lymph node dissection			
	22.4±10.4	20.5±9.61	0.52

Table 3. Comparison of IIQ-7, UDI-6, and ICIQ-SF scores between the test and control groups before surgery and 1 and 12 months after surgery

	Test group	Control group	*p*-value
IIQ-7 (preoperative)	4.06±1.93	4.30±1.76	0.51
IIQ-7 (1 month postoperative)	8.64±4.96	4.36±1.69	<0.001
IIQ-7 (12 months postoperative)	12.8±4.96	4.42±1.61	<0.001
UDI-6 (preoperative)	4.04±1.57	4.50±1.18	0.10
UDI-6 (1 month postoperative)	7.14±5.25	4.56±1.12	<0.001
UDI-6 (12 months postoperative)	10.6±6.68	4.54±1.14	<0.001
ICIQ-SF (preoperative)	7.14±4.11	8.46±4.59	0.13
ICIQ-SF (1 month postoperative)	11.7±6.14	8.52±4.59	0.004
ICIQ-SF (12 months postoperative)	16.02±6.87	8.56±4.57	<0.001

IIQ-7: incontinence impact questionnaire-7; UDI-6: urogenital distress inventory-6; ICIQ-SF: international consultation on incontinence questionnaire-short form

and adjuvant treatments based on UDI-6, IIQ-7, and ICIQ-SF questionnaires administered 1 week before surgery and during follow-up visits. We excluded patients who underwent radical hysterectomy for cervical cancer (CC). Although nerve-sparing surgery is performed on patients with CC, radical hysterectomy affects bladder function via a combination of intraoperative trauma to the bladder, anatomical displacement following the removal of the uterus and its supporting ligaments, and damage to the pelvic nerves during paravaginal dissection.[8]

Surgery for cancer was an independent risk factor for UI. Our results are in line with those of a previous study by Neron et al.[9] that evaluated postoperative pelvic floor dysfunction in patients who underwent surgery for gynecological malignancies and benign disease. Patients who underwent hysterectomy for cancer had an increased risk for incontinence than those who underwent hysterectomy for benign disease. Because the vaginal cuff is not fixed when a hysterectomy is performed for cancer, pelvic floor dysfunction may result. Incontinence develops more commonly in cancer patients because of bladder dysfunction due to nerve damage.[10]

There were significant differences in the type of operation between the test and study groups. Laparoscopy was performed

Table 4. IIQ-7, UDI-6, and ICIQ-SF scores in the test group and control group before surgery and 1 and 12 months after surgery

Test group				
	Preoperative	**1 month postoperative**	**12 months postoperative**	***p*-value**
IIQ-7	4.06±1.93	8.64±4.96	12.8±4.96	<0.001
UDI-6	4.04±1.57	7.14±5.25	10.6±6.68	0.03
ICIQ-SF	7.14±4.11	11.7±6.14	16.02±6.87	<0.001
Control group				
IIQ-7	4.30±1.76	4.36±1.69	4.42±1.61	0.126
UDI-6	4.50±1.18	4.56±1.12	4.54±1.14	0.604
ICIQ-SF	8.46±4.59	8.52±4.59	8.56±4.57	0.082

IIQ-7: incontinence impact questionnaire-7; UDI-6: urogenital distress inventory-6; ICIQ-SF: international consultation on incontinence questionnaire-short form

Table 5. Frequency of incontinence and its types after the operation in the test and control groups

	Test group	**Control group**	***p*-value**
Incontinence			
Yes	15 (43.2%)	4 (21.1%)	
No	35 (56.8%)	46 (78.9%)	
Type of incontinence			0.317
SUI	9 (64.3%)	3 (60.0%)	
Urge	2 (14.3%)	0 (0%)	
Mixed	3 (21.4%)	1 (20%)	

SUI: stress urinary incontinence

Table 6. Univariate and multivariate analyses of group, brachytherapy, external beam radiotherapy + brachytherapy, chemotherapy + radiotherapy, chemotherapy, and surgery type

Parameter	**Univariate analyses**			**Multivariate analyses**		
	Hazard ratio	**95% CI**	***p*-value**	**Hazard ratio**	**95% CI**	***p*-value**
Group	5.4	1.6-17.6	0.002	5.35	1.2-23.5	0.02
BRT	2.2	1.5-2.8	0.01	1.13	0.7-3.7	0.99
EBRT	5.0	1.28-19.4	0.02	2.43	0.47-12.4	0.28
KTRT	4.15	0.24-69.5	0.33	1.29	0.06-25.0	0.86
KT	3.85	1.15-12.8	0.03	1.62	0.3-6.9	0.51
Surgery type (LS or LT)	1.7	0.6-4.9	0.31	1.8	0.3-4.12	0.79

CI: confidence interval; EBRT: external beam radiation therapy; KTRT: chemoterapy + radiotherapy; KT: chemotherapy; LS: laparoscopic; LT: laparotomic

in 88.0% and 40.0% of patients in the control and test groups, respectively. In multivariate analyses of variance, operation type was not evaluated as an independent risk factor for UI. Skorupska et al.[11] evaluated the effects of hysterectomy type on postoperative UI in 392 women and found that hysterectomy, but not the type of surgery, was a risk factor for UI.

In the test group, IIQ-7, UDI-6, and ICIQ-SF scores were significantly higher 1 and 12 months after surgery than preoperative scores, whereas in the control group there were no significant differences between preoperative and postoperative scores. Ziętek-Strobl et al.[12] evaluated the effects of surgery according to surgical indication and adjuvant treatment on genitourinary symptoms based on preoperative and 6-month postoperative IIQ-7 and UDI-6 scores and found an increase in scores, similar to our study. Similarly, Nakayama et al.[13] compared the quality of life of patients who underwent surgery and adjuvant treatment for ovarian cancer and those who underwent hysterectomy for non-oncological causes 3, 6, 9, and 12 months after surgery.

Christiansen et al.[14] found no significant change in UI scores during long-term follow-up among women who underwent hysterectomy for benign causes.

Nosti et al.[15] evaluated pelvic floor dysfunction in patients who underwent surgery for endometrial cancer and found that postoperative incontinence was common and negatively affected quality of life. Urinary system dysfunction commonly occurs in patients treated for ovarian cancer.[10] Similar to previous studies, incontinence developed after surgery in 15 (43.2%) and 4 (21.1%) patients in our test and control groups, respectively, with a significantly higher rate in the former group than the latter one. This may be due to the effects of combined cancer treatments on the urinary system.[16]

Stress, urge, and mixed UI developed in 9 (64.3%), 2 (14.3%), and 3 (21.4%) patients in the test group, respectively. Stress and mixed UI developed in 3 (60.0%) and 1 (20.0%) patients in the control group, respectively. There were no significant differences between the groups in terms of type of incontinence. In a meta-analysis by Duru et al.[17], urodynamic studies after hysterectomy in 80 patients showed no significant differences between types of incontinence. The lack of difference between types of incontinence may be due to the separation of the uterus and cervix from the pelvic floor support tissues due to the operation, malfunction in the urethral sphincter mechanism after damage to the distal branches of the pudendal nerves, or changes in the urethra and bladder neck support.[18]

Radiation kills cells by delivering high-energy particles to the cancer; however, damage to adjacent normal tissue, such as the bladder or gastrointestinal tract, is ineluctable.[16] The bladder is at risk during radiation therapy for gynecological malignancies. The urinary complications of radiation therapy include dysuria, hematuria, stress UI, urge UI, and radiation cystitis.[19] Chemotherapy uses cytotoxic drugs to induce apoptosis in tumor cells. Adverse effects of chemotherapy on the urinary system include urinary tract infections, glomerulonephritis, and renal failure due to drug toxicity, which may lead to UI.[20]

Patients who received BRT and radiotherapy had higher scores than other patients. Herwig et al.[21] investigated late urinary effects after treatment of stage 1 endometrial cancer. UI was more common in patients who received combined BRT and radiotherapy than in patients who received BRT only, similar to our results. Oplawski et al.[10] examined the effects of combination therapy for endometrial or ovarian cancer on urinary system dysfunction and quality of life. Patients who underwent surgery for endometrial cancer had a 2-fold higher risk for UI if they received BRT compared to those who received adjuvant chemotherapy. These results are similar to those of the present study. Questionnaire scores were significantly higher among patients who received BRT only than those who received chemotherapy only. Similarly, in our study, Zafarnia et al.[22] found that genitourinary symptoms had a greater effect on UI and quality of life in patients who received RT than in patients who received chemotherapy.

In total, 13 (81.3%) of the 16 patients with ovarian cancer received chemotherapy, whereas 3 (18.8%) did not receive additional adjuvant treatment. UI was more common and quality of life was worse among patients who received chemotherapy than those who did not receive chemotherapy. Oplawski et al.[10] examined the effects of adjuvant chemotherapy and surgery on urinary system dysfunction and quality of life among patients with ovarian cancer. UI was more common and quality of life was better, as evidenced by higher UDI-6 and IIQ-7 scores, among patients who received adjuvant chemotherapy than those who underwent surgery for ovarian cancer only.

Study Limitations

This study has a few limitations, including a small sample size and short follow-up duration. Yet this single-center case-control study included patients who underwent surgery by a single surgeon, which indicates the usefulness of our study.

Conclusion

Genitourinary symptoms should be evaluated in patients undergoing staging surgery for cancer, in particular those who plan to receive adjuvant treatment after the staging surgery. Such patients should be monitored for the development of urinary incontinence.

ETHICS

Ethics Committee Approval: The study was approved by the Local Research Ethics Committee of Muğla Sıtkı Koçman University (220096/86).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Contributions

Surgical and Medical Practices: İ.A.Ö.; Concept: B.S., K.G., İ.A.Ö.; Design: B.S., K.G.; Data Collection or Processing: B.S., K.G.; Analysis or Interpretation: B.S., K.G.; Literature Search: B.S.; Writing: B.S., İ.A.Ö.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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Female sexual function outcomes in patients operated for pelvic floor dysfunction: Comparison of synthetic mesh with native tissue repair

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ABSTRACT

Objectives: We aimed to evaluate the impact of urogynecologic mesh implantations on sexual function using female sexual function index (FSFI) questionnaire

Materials and Methods: In this cross-sectional retrospective study, a total of 187 patients which found to have pelvic organ prolapse or stress urinary incontinence (SUI) surgery were investigated between 2015 and 2022. Patients whose main complaint was SUI and had tension free vaginal tape operation (n=21) or transobturator tape operation (n=17) constituted the "Midurethral mesh group" (n=38). Those who had cystocele repair with double obturator trapezoid mesh formed the "Cystocele repair with mesh" group (n=35). Patients who had cystocele repair with natural tissue repair without any mesh implant in the vagina or elsewhere in the pelvis constituted the "Natural tissue repair" group (n=79). The patients were informed about the study and their consent was obtained.

Results: The mean time elapsed since surgery till FSFI measurement was 32±6.5 months in Midurethral Mesh group; 34±7.1 months in the "Cystocele repair with mesh group and 33±7 months in the natural tissue repair group (p>0.05). Total FSFI scores 22.8±6.8, 22.2±7.5, 22.5±7.9 and the frequency of patient with scores lower than 26.5, which is the cut-off for disfunction, was 27 (71.1%), 20 (57.1%) and 47 (59.5%) similar in the three groups (p>0.05). The FSFI subdomain scores such as desire, arousal, lubrication, orgasm, satisfaction, pain was similar in the three groups (p>0.05 for all comparisons).

Discussion: Our study demonstrated that surgical repair of symptomatic pelvic organ prolapse and SUI surgery using mesh implants or natural tissue repair had similar results of major parameters of sexual function after surgery.

Keywords: Female sexual function after vaginal surgery; pelvic organ prolapse; quality of life; transobturator mesh implants

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INTRODUCTION

Female pelvic floor disorders such as urinary incontinence and pelvic organ prolapse have life altering impact on women's lives. One in four women present any one of the symptoms of pelvic floor disorders.[1] Aging women has increase in pelvic floor disorders and decrease in sexual activity.[2,3] Women with pelvic organ prolapse feel less feminine and sexually attractive and 31% report that symptoms of pelvic organ prolapse interfere with sexual activity.[4,5] Urinary incontinence has 25% prevalence among women and one out of five women is worried about urine loss during sexual activity.[6,7]

Female sexuality is related to age, education, social network, marital status and presence of gynecologic pathology such as pelvic floor disorders.[8] The treatment of pelvic floor disorders includes surgical approach using synthetic mesh or native tissue. There has been debate on safety of transvaginal mesh use since 2008 warning of Food and Drug Administration and resulted in classification of mesh use as high risk for impaired sexual function and *de novo* dyspareunia.[9,10]

In the present study female sexual function index (FSFI) form developed by Rosen et al.[11] and validated for the Turkish community was used.[12] We assessed and compered the sexual function of women after mesh surgery for urinary incontinence and pelvic organ prolapses compared to women with native tissue repair surgery for pelvic organ prolapses.

MATERIALS AND METHODS

In this cross-sectional study, woman who had pelvic organ prolapse surgery or stress urinary incontinence (SUI) surgery were called for control visit for pelvic examination and applied FSFI. The patient files of patients were searched between 2015 and 2022 in Alanya Training and Research Hospital and Private Aktif Kocaeli Hospital. A total of 187 patients were found to have pelvic organ prolapse or SUI surgery. The patients were informed about the study and their consent was obtained. Those with isolated posterior rectocele repair only (n=9), concomitant malignant disease (n=7), no sexual partner (n=11) and lost to follow-up (n=8) were excluded and 152 women were included in the study. Local ethical approval was obtained (ALKÜ-KAEK-28/12/22.15-04)

The descriptive data, patient history, operative outcomes, concomitant procedures were obtained from the patient and patient files. All patients had complete gynecological pelvic examination with pelvic ultrasound scan transvaginally. Patients whose main complaint was SUI and had tension free vaginal tape (TVT) operation (n=21) or transobturator tape operation (n=17) constituted the midurethral mesh group (n=38). Those who had cystocele repair with double obturator trapezoid mesh formed the "Cystocele repair with mesh" group (n=35). Patients who had cystocele repair with natural tissue repair without any mesh implant in the vagina or elsewhere in the pelvis constituted the "Natural tissue repair" group (n=79). In all procedures macroporous polypropylene meshes were used (Duzey SUT cystocele and Duzey SUT vaginal tape meshes, Duzey Medical, Türkiye).

The primary outcome measure of our study is sexual function. FSFI is a clinical tool to assess sexual function in the general population. It consists of domains such as desire, lubrication, orgasm, sexual contentment and pain. The questionnaire is not planned to be used as a diagnostic tool. Moreover, it cannot surpass a holistic sexual evaluation since it does not measure sexual experiences, knowledge or interpersonal differences. The gained results are directly proportional to sexual function that provide an evaluation window. The higher the score the better sexual function. Only pain domain uses an inverse relation as to the less pain yielding higher score. The results are displayed within the range of 2 to 36 points.

The secondary outcome measure was evaluation of efficacy of pelvic floor repair by mesh, clinical performance and, complication rates. All women in the study were evaluated preoperatively for general medical history, sexual history, physical examination, urodynamic studies and FSFI questionnaires. Pelvic organ prolapse was measured by POP-Q system. POP-Q system consists of 9 measurements. The anterior compartment is characterized by Aa and Ba, the vaginal apex by C and D and the posterior compartment by Ap and Bp. According to this classification, stage 0 is defined as nearly perfect anatomic support with no prolapse. Stage I is defined as Aa, Ba, Ap, Bp and C being 1 cm above the hymen. Stage II is defined as the leading edge of the prolapse being within 1 cm of the hymen. Stage III is defined as the leading edge of the prolapse being 11 cm beyond the hymen, with the difference between the leading edge and the total vaginal length being less than 12 cm. Stage IV is defined as a difference of more than 12 cm between the leading edge and the total vaginal length. All examinations were done at dorsal lithotomy position. Bladder was emptied before vaginal examination. Sims speculums were used.

Statistical Analysis

Statistical analysis was performed using SPSS software version 21 (SPSS Inc. Chicago, IL, USA). Data are expressed as means and standard deviation of the mean or as numbers and percentages. One-Way ANOVA and Tukey test as post-hoc test was used for continuous variables. Pearson chi-square or likelihood ratio was used to compare percentages wherever appropriate.

RESULTS

Selected demographic data, voiding abnormality frequency previous hysterectomy and current status of pelvic organs are summarized in Table 1. The age, gravida and parity were similar in all groups. In preoperative findings anterior vaginal wall prolapse, uterine prolapse and history of hysterectomy was less frequent in the Midurethral mesh group compered to Cystocele repair with mesh or natural tissue repair groups. The frequency of posterior vaginal wall was similar in the three groups.

The pelvic organ prolapses classification prior to surgery is presented in Table 2. According to POP-Q classification none of the patients in cystocele repair groups either with mesh or with normal tissue had a case with POP-Q stage 0 or 1.

Concomitant surgeries in the three groups are presented in Table 3. No midurethral sling was done Natural tissue repair group, no Burch operation was done in Midurethral sling group and Cystocele repair with mesh group.

The clinical and functional outcomes after operation for pelvic organ prolapse is presented in Table 4. The frequency of acute urine retention, vaginal infections, voiding dysfunction, dyspareunia and constipation were similar in the three groups.

Table 1. Demographics of the patient's population

Variables	Midurethral mesh n=38	Cystocele repair with mesh n=35	Natural tissue repair n=79	p
Age (mean ± SD)	52.5±9.7	54.3±12.9	56.3±11.3	0.23
Gravida (mean ± SD)	4.1±2.4	3.9±2.1	4.2±2.3	0.7
Parity (mean ± SD)	3.4±2.1	3.0±1.4	3.4±2.0	0.6
Surgical history (%), and preoperative findings:				
Prolapse of the anterior vaginal wall	21 (55.3)	35 (100)	56 (70.9)	<0.05
Prolapse of the posterior vaginal wall	11 (28.9)	17 (48.6)	32 (40.5)	0.2
Uterine prolapse	5 (13.2)	12 (34.3)	46 (58.2)	<0.05
Hysterectomy	5 (13.2)	11 (31.4)	47 (59.5)	<0.05
Voiding abnormality, (%):				
SUI	38 (100)	14 (40)	19 (24.1)	<0.05

SD: standard deviation; SUI: stress urinary incontinence

Table 2. Pelvic organ prolapses classification prior to surgery

POP-Q, (%)	Midurethral mesh n=38	Cystocele repair with mesh n=35	Natural tissue repair n=79
0-1	10 (26.3)	0	0
2	20 (52.6)	12 (34.3)	26 (32.9)
3	4 (10.5)	11 (31.4)	8 (10.1)
4	4 (10.5)	12 (34.3)	45 (57)

Table 3. Characteristics of the surgery

Concomitant procedure, (%)	Midurethral mesh n=38	Cystocele repair with mesh n=35	Natural tissue repair n=79
Vaginal hysterectomy	**7 (18.4)**	12 (34.3)	32 (40.5)
Posterior colporrhaphy	5 (13.2)	2 (5.7)	12 (15.2)
Midurethral sling	38 (100)	2 (5.7)	0
Uterine/vaginal vault suspension	5 (13.2)	11 (31.4)	47 (59.5)
Sacrospinous ligament fixation	0	18 (51.4)	47 (59.5)
Perineal correction	6 (15.8)	7 (20)	11 (13.9)
Burch	0	0	9 (11.4)

None of the groups had inadvertent bladder entry and only one case in Cystocele with Mesh repair experienced mesh exposure.

The FSFI scores after surgery for pelvic organ prolapse is presented in Table 5. The mean time elapsed since surgery till FSFI measurement was 32±6.5 months in midurethral Mesh group; 34±7.1 months in the natural tissue repair group (p>0.05). The subdomain scores such as desire, arousal, lubrication, orgasm, satisfaction, pain was similar in the three groups. Total FSFI scores and frequency of patient with scores lower than 26.5 which is the cut-off for dysfunction was similar in the three groups.

The anatomical outcomes and overall patient satisfaction are given in Table 6. The mean patient satisfaction over 5 Likert scale was 4±1.3 in midurethral mesh group, 3.8±1.3 in cystocele repair with mesh group and 4±1.3 in natural tissue repair group. Repeat pelvic organ prolapsus was 7.9%; 8.6% and 10% percent respectively in the three group and SUI was 10.5%; 14.3% and 13.9%.

Table 4. Clinical and functional outcomes after operation for pelvic organ prolapse

Post-operative complication, (%)	**Midurethral mesh n=38**	**Cystocele repair with mesh n=35**	**Natural tissue repair n=79**	***p***
Acute urine retention	7 (18.4)	6 (17.1)	7 (8.9)	0.26
Inadvertent bladder entry	0	0	0	-
Vaginal infections	3 (7.9)	3 (8.6)	6 (7.6)	0.94
Mesh exposures	0	1 (2.9)	0	0.9
Voiding dysfunction	1 (2.6)	4 (11.4)	7 (8.9)	0.34
Dyspareunia	3 (7.9)	3 (8.6)	6 (7.6)	0.9
Constipation	4 (10.5)	4 (11.4)	10 (12.7)	0.94

Table 5. Follow-up of FSFI after surgery for pelvic organ prolapse

Variable (mean ± SD)	**Midurethral mesh n=38**	**Cystocele repair with mesh n=35**	**Natural tissue repair n=79**	***p***
Desire	3.2±1.1	3.6±1.3	3.6±1.5	0.3
Arousal	3.5±1.4	3.8±1.7	3.8±1.7	0.7
Lubrication	3.4±1.3	2.8±1.4	3.0±1.6	0.2
Orgasm	3.7±1.7	3.3±1.9	3.5±1.8	0.6
Satisfaction	4.0±1.3	3.8±1.3	4±1.3	0.8
Pain	4.7±1.7	4.5±2	4.4±1.9	0.8
Total score	22.8±6.8	22.2±7.5	22.5±7.9	0.6
FSFI <26.5, (%)	27 (71.1)	20 (57.1)	47 (59.5)	0.39

SD: standard devation; FSFI: female sexual function index

Table 6. Anatomical outcomes and overall patient satisfaction evaluated according to Likert scale

%	**Midurethral mesh n=38**	**Cystocele repair with mesh n=35**	**Natural tissue repair n=79**	***p***
Very unsatisfied	3 (7.9)	3 (8.6)	7 (8.9)	
Unsatisfied	5 (13.2)	4 (11.4)	5 (6.3)	
Neutral	1 (2.6)	2 (5.7)	10 (12.7)	
Satisfied	12 (31.6)	12 (34.3)	22 (27.8)	
Very satisfied	17 (44.7)	14 (40)	35 (44.3)	0.7
Mean satisfaction score ± SD	4±1.3	3.8±1.3	4±1.3	0.8
POP-Q ≥3-4	3 (7.9)	3 (8.6)	8 (10.1)	0.91
SUI	4 (10.5)	5 (14.3)	11 (13.9)	0.85

SD: standard deviation; SUI: stress urinary incontinence

DISCUSSION

The main finding of this study is similar FSFI scores of women after midurethral mesh placement or cystocele repair with mesh compared to native tissue repair group in cases with pelvic floor dysfunction. These outcomes will be discussed cautiously as our study group has no FSFI scores preoperatively. Also, there are many confounding variables such as menopausal status, age, the presence of pelvic floor dysfunction, concomitant procedures like hysterectomy that might affect the 57 to 71% sexual dysfunction rate in our study population.

The FSFI scale based sexual dysfunction was reported to affect between 43 to 71% of women in different populations.[13,14] As sexuality might be affected by cultural values, taboos and social norms Turkish women showed that. Overall incidence of sexual dysfunction ranges between 46.9 to 78% in different regions of Türkiye with different study populations.[15-18] A closer look at the subgroup of patients between 45-57 years revealed a more uniform incidence of 65.9%, 67.9%, 70.9%, 72.7%, 78% of in the mentioned studies.[15-18] The women with a history of premature menopause or surgical induction of menopause had the highest incidence of female sexual dysfunction of 783.[18] The mean age of our patient population is early fifties and sexual dysfunction incidences we report as 57.1 and 59.5% in mesh or native tissues repair of cystocele are lower than the background population where as 71% in midurethral mesh group is similar to background population incidence. We can assume that the sexual dysfunction incidence after operations for pelvic floor dysfunction are in accordance or lower than the reported population studies.

The prevalence of dyspareunia has been reported to be 7.8-47.2% in Turkish studies.[19,20] The latter higher incidence is a specialized sexual problem clinic-based study. The reported dyspareunia rate of 7.6%, 7.9% and 8.6% after operations in our study group is similar to each other and the population based reports.[19] The dyspareunia after pelvic floor dysfunction was related vaginal narrowing, mesh exposure or levator plication.[21] The reported incidence of denova dyspareunia was 7% after mesh surgery for anterior comportment compared with 4% dyspareunia with native tissue repair which was not statistically significant.[21,22] None of the patients in our study had levator plication and we have found 2.9% prevalence of mesh exposure in cystocele repair with mesh group.

Regarding the concomitant procedures applied in our study group. It is hard to say which of the specific procedure might cause dyspareunia.

Another source of concern is the effect of hysterectomy is high in our study population with a significantly higher rate in native tissue repair group compared to mesh groups. Several randomized controlled trials found improvement in sexual function after either total or subtotal hysterectomy.[23,24] In another study found an improvement in orgasm after hysterectomy for pelvic organ prolapses.[25]

Study Limitations

The limitations and warnings on transvaginal mesh surgeries need to be revaluated. In a systemic review of 26 studies. Antosh et al.[26] compared transvaginal mesh use with native tissue repair and found no difference in preoperative and postoperative sexual activity, dyspareunia, sexual function assessed via PISQ-12 scores.

CONCLUSION

Our study yielded similar results with FSFI based evaluation of sexual function which is validated and well studies in Turkish women. The sexual dysfunction in our study group is similar to the women population. Ageing, presence of pelvic floor dysfunction are more profound factors to affect the postoperative sexual dysfunctions rather than the surgical technique used to treat pelvic floor dysfunction.

ETHICS

Ethics Committee Approval: The patient files of patients were searched between 2015 and 2022 in Alanya Training and Research Hospital and Private Aktif Kocaeli Hospital. Local ethical approval was obtained (ALKÜ-KAEK-28/12/22.15-04).

Informed Consent: The patients were informed about the study and their consent was obtained.

Peer-review: Externally peer-reviewed.

Contributions

Concept: E.Ç., E.K.; Design: E.Ç., E.A.; Data Collection or Processing: B.A.; Analysis or Interpretation: E.Ç., G.K.; Literature Search: B.A.; Writing: E.Ç., E.K.

DISCLOSURES

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The management of a bicycle trauma leading to vulvar tissue loss: A case report

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ABSTRACT

Vulvar tissue losses due to trauma are rare and few cases have been reported in the literature. In cases with tissue loss surgical intervention is necessary. Not only the vulvar reconstruction but also tissue perfusion with blood is utmost important. We present the case of a patient with vulvar tissue loss due to bike accident and the management of the patient.

Keywords: Vulvar trauma; vulvar tissue loss; superficial femoral artery perforator flap

INTRODUCTION

After the adolescent period, the fatty tissue is deposited in mons pubis and labia majora providing a protection to traumas. Non-obstetric traumas to the abundant blood vessels and nerve endings in these areas can lead to different clinical problems such as hematoma, lacerations, tears, tissue loss, chronic pain an even itching. However, the non-obstetric vulvar injury incidence is 3.7%.[1] Injuries are frequently due to falling astride a firm object, consensual coitus, sexual assault, vigorous coitus, acts of physical aggression cold waxing, tight clothing, insertion of foreign bodies and self-manipulation.[1,2] Vulvar tissue loss is very rare compared to the vulvar hematomas and basically is a result of penetrating trauma to the region.

CASE REPORT

A 24-years-old female patient admitted to our unit 1 week after falling off bike. Her vulvar examination revealed an infected discharge and necrotic appearance with a tissue loss of approximately 10x3 cm, including the left labia minora. Also, there were stitches visible over the wound that had been put in the center which the patient applied soon after the accident (Image 1). Antibiotherapy was started. Tetanus vaccine and tetanus IG prophylaxis were applied. The wound cleaning and local debridement were performed upon admission on daily basis. As a result of daily dressings with rifocin and necrotic tissue debridements, the wound turned out to be clean on the 7th day of admission (Image 2). On the 8th day of patients's admission,

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the patient was operated for reconstruction. The patient and relatives gave informed consent to surgery and video recording.

The superficial femoral artery perforator (SFAP) flap was harvested measuring 10x3 cm in ovoid shape from the inferior region of gracilis muscle. The flap was advanced 4 cm towards the vaginal introitus and was sutured to the edge of the vaginal introitus with 3/0 PDS. Moreover, the rest of the flap was sutured to the healty skin tissue with 4-0 rapid polyglactin (Image 3). A 10F hemovac drain was placed under the flap. The patient was discharged on postoperative 5th day without any problem.

The follow-up visits on first week (Image 4) and first month (Image 5) after discharge showed no signs of infection and rejection. Besides she had no discomfort during walking due to flap. She was very happy with the cosmetic and anatomical result that have been achieved.

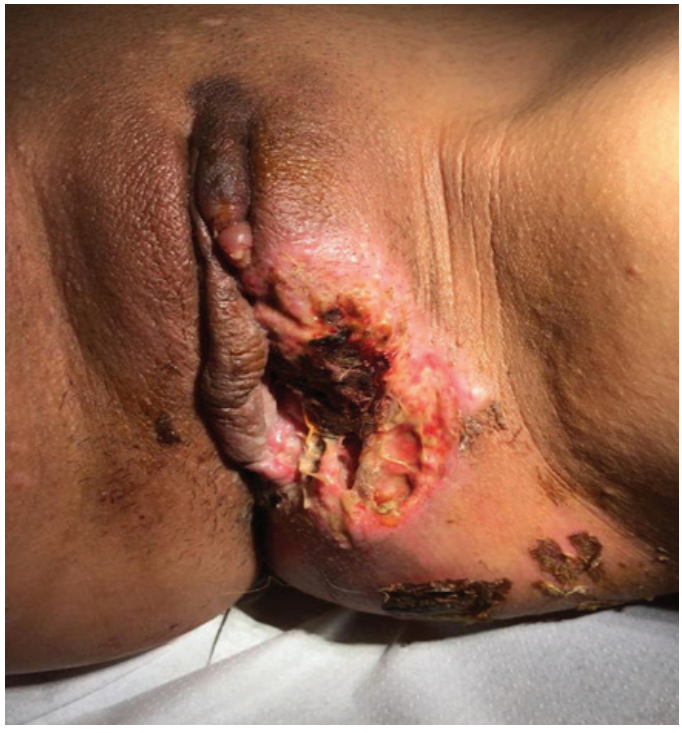

Image 1. The apperance of the vulva upon admission of the patient. Necrotic tissues and profuse discgharge as well as stitches were visible

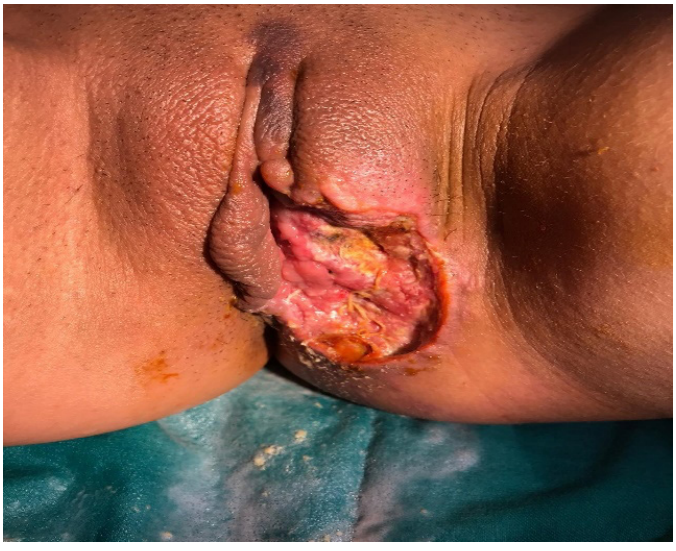

Image 2. The wound is seen as clean after daily dressings and antibiotic treatment

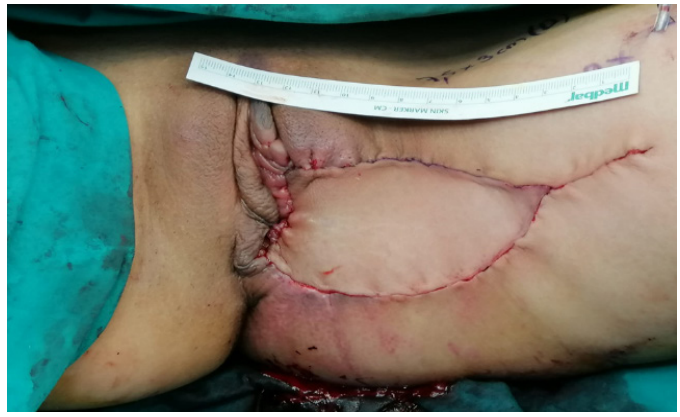

Image 3. The The superficial femoral artery perforator flap which was harvested from the inferior region of the gracilis muscle was advanced towards the vaginal introitus in order to cover the defective area (the advancement of the flap was 4 cm)

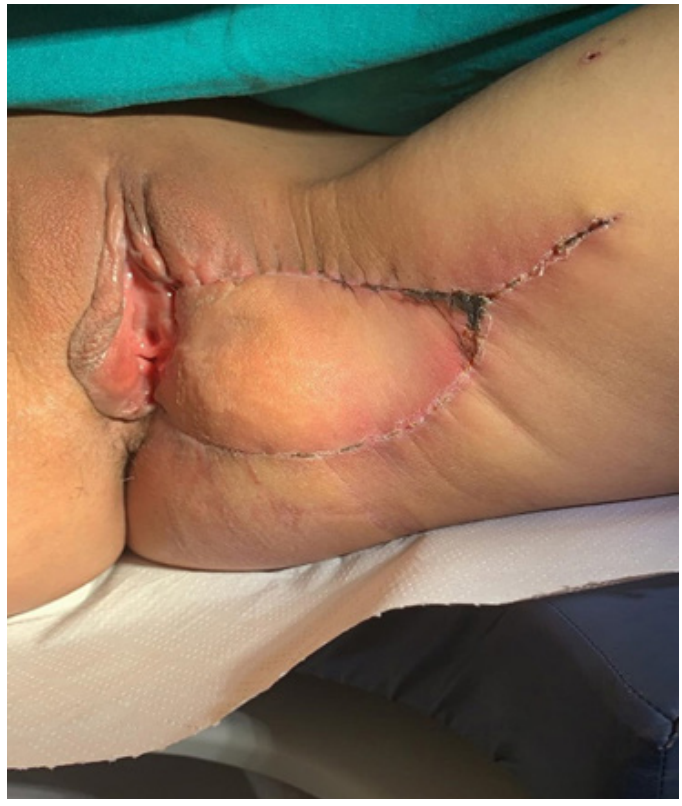

Image 4. The view on postoperative 7th day. There was no sign of infection or rejection of the flap

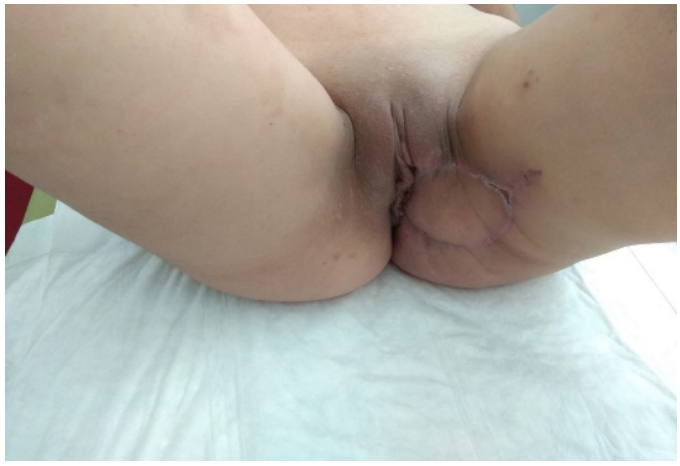

Image 5. The view on postoperative 1 month. The cosmetic and anatomical results were very good

DISCUSSION

Vulvar lesions necessiating surgical intervention represent 0.8% of all gynecologic emergencies.[1] The vulva contains loose connective tissue and smooth muscles. The blood perfusion is mainly from the pudendal artery, which branches off the internal iliac artery. The injury to labial branches of the internal pudendal artery, may cause significant vulvar hematomas or bleeding. In our case, the patient fell off the bike and a large tissue defect roughly measuring 10x3 cm was seen. No hematoma was observed. However; an extensive swelling was noted that should be related to the low resistance of the subcutaneous tissues in vulva.[3] Generally, the bleeding is usually seen beneath the pelvic fascia and the levator ani. However, if the hematoma is on the pelvic fascia, it can spread underneath the Poupart's ligament and reachs up to the renal fossae retroperitoneally.[4]

The management of vulvar soft tissue defects has been well defined. According to the agorithm; if the defect is <2 cm in diameter wound closure without flap can be carried out; however if the defect is >2 cm, then for cosmetic and functional reasons flap surgery must be considered.[5] Although there are different flap techniques; perforator flaps have been gaining popularity. With the development of microvascular surgery, and further understanding of the anatomic vasculature of the SFAPs, its utilization as a donor site likely appears to increase dramatically.[6] The superficial femoral artery supplies the distal two thirds of the medial thigh as well as portions of the proximal third of the anteromedial thigh.[7] In our case; we used the SFAP flap with a great success.

CONCLUSION

The treatment of the penetrating vulvar traumas leading to tissue loss necessitates expertise.

Large vulvar defects should be treated with flap and basically perforator flaps in the region provide better results.

ETHICS

Informed Consent: The patient and relatives gave informed consent to surgery and video recording

Peer-review: Internally and externally peer-reviewed.

Contributions

Surgical and Medical Practices: M.A., A.A.S.; Concept: A.A.S.; Design: A.A.S.; Data Collection or Processing: M.A., A.A.S., T.H.; Analysis or Interpretation: A.A.S.; Literature Search: T.H.; Writing: T.H.

DISCLOSURES

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Vaginal tactile imaging: A review

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ABSTRACT

Vaginal Tactile Imaging is a novel technology that creates a visual map of the female pelvic floor based on its biomechanical properties. The vaginal tactile imager is a medical device built on this technology to assist clinicians in diagnosis and prognosis of pelvic floor conditions and treatment from detailed characterization of vaginal tissue elasticity, pelvic support and function. This information is presented in the form of tactile images, a format in which pressure mapping is combined with spatial dimensions. The dynamic pressure patterns are combined using two opposing areas along the vaginal walls during Valsalva maneuver, voluntary and reflex muscle contraction, and involuntary relaxation. Based on these measurements, the biomechanical integrity score of the pelvic floor was developed and introduced to facilitate clinical interpretation of the complex data. This article begins with a brief overview of the tactile imaging for a broad spectrum of applications, clinical research findings and their respective impact. Then the article focuses on the evolution of the technology and its progressive development for the female pelvic floor disorders characterization and diagnostics, including evaluation of surgical intervention. Finally, future possibilities for tactile imaging are discussed, including applications in obstetrics and a fusion with ultrasound imaging.

Keywords: Vaginal tactile imaging; biomechanical mapping; biomechanical integrity score; tissue elasticity; pelvic support; pelvic muscles; pelvic organ prolapse; urinary incontinence

INTRODUCTION

Pelvic organ prolapse (POP) is a highly prevalent condition affecting 40-50% of women during their lifetimes.[1-3] Urinary incontinence (UI) affects up to 48% of women.[4,5] Both POP and UI are more common in women than in men, and their prevalence is increased with age.[3-6] POP is often associated with concomitant pelvic floor disorders, UI and fecal incontinence, pelvic pain, voiding, and sexual dysfunctions.[7] These conditions cause significant morbidity beyond the physical and the quality-of-life impacts.[8,9]

The true etiology of POP and UI and variations observed among individuals are not entirely understood. These disorders are thought to share common pathogeneses, weakening (elasticity changes) of the connective support tissues and pelvic floor muscle dysfunction.[10-22] The lifetime surgery risk for either UI or POP in women is about 20%.[23,24] A POP surgical failure rate

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of 61.5% for uterosacral ligament suspension and 70.3% for sacrospinous ligament fixation groups in a representative study was reported.[25] The estimated annual cost of POP surgeries and UI care in the U.S. is about $24 billion.[26,27]

With the global population getting older the pelvic floor diseased conditions will increase in prevalence.[3,28] It is projected that by 2050, 43.8 million women, or nearly 33% of the adult U.S. female population, would be affected by at least one troublesome pelvic floor disorder.[6,29] Additionally, due to the Coronavirus disease-2019 pandemic a large number of the population has been unable to attend routine appointments increasing the likelihood of undiagnosed pelvic floor conditions.

The current clinical practice for assessment of POP and UI is generally limited to the evaluation of surface anatomy by manual palpation. In severe or complicated cases, ultrasound, magnetic resonance imaging (MRI), and X-ray imaging may be used for additional evaluation. Bladder and rectum function tests, such as urodynamics, manometry, or defecography might also be employed.[7,30-34]

Conventional ultrasound is available for the imaging of pelvic floor organs. Perineal or translabial, transvaginal, and abdominal ultrasounds are increasingly used for assessing POP and UI.[35-38] Ultrasound, as a part of the diagnostic workup, enables morphological and dynamic assessment of the lower urinary tract. In the last decade, transrectal ultrasound gained ground for assessing the female urogenital organs.[39]

Despite criticisms that MRI is an expensive modality, cost-analysis studies are demonstrating utility for MRI in surgical decision-making trees for patients at risk for POP repair failure. Novel measures such as anterior pelvic area and levator volumes are proposed.[40] Diffusion-weighted imaging, dynamic contrast-enhanced MRI, and susceptibility-weighted imaging were developed for evaluation of endometriosis, local staging of cervical and endometrial cancers, and assessment of nodal and peritoneal metastases.[41] Dynamic MRI is used for the assessment of fecal incontinence.[42,43]

Biofeedback with vaginal pressure measurements (air balloon or 1-2 pressure sensors) has been widely utilized in the treatment of pelvic floor dysfunctions, mainly by promoting patient learning about muscle contraction.[44,45] Urodynamics records pressure measurements in the bladder, urethra, vagina, and rectum with catheters. Despite technical and procedural advances in urodynamics, the role of urodynamics in women with UI remains controversial.[46-49]

None of the above-listed techniques produce biomechanical mapping (stress-strain and functional) of the female pelvic floor structures with accurate anatomical identification.

Elastography, or elasticity imaging, involves the application of a stress to soft tissue and measurement of the resulting tissue mechanical response. There are several methods available to apply stress to a tissue and to measure the resulting response. The stress can be generated from an external source such as a compression probe, an external vibrator, acoustic radiation force, or physiological sources of motion (cardiac motion and fluid flow). The most common measurement methods of tissue response (strain) include ultrasound, MRI, and mechanical/tactile imaging.[50,51] The strain ultrasound is not capable of soft tissue characterization on an absolute scale without stress data. Shear wave elastography seems too complicated for intravaginal application due to the heterogeneity of the tissues.[52-55] The MRI elastography is a complex technology with a relatively high cost and low resolution.[56-58] A mechanical imaging (MI) reconstructs form and elasticity distribution of an organ or object based on pressure patterns of the object surface and expected anatomy and pathology of the object.[59] A tactile imaging probe translates stress data from the surface of deformed soft tissue into a 2D tactile image, assessing tissue biomechanical parameters.[60,61] It also provides high-definition pressure response patterns at Valsalva maneuver, voluntary and reflex pelvic muscle contractions.[14] Tactile imaging is a relatively simple and inexpensive technique.[62] With the increasing need for diagnostics and no practical method for biomechanical assessment of the female pelvic floor, tactile imaging may have a profound impact on women's healthcare.

Definitions

MI is a modality of medical diagnostics based on reconstruction of tissue structure and viscoelastic properties using mechanical sensors. The essence of MI is the solution to an inverse problem using the data of stress patterns on the surface of tissue compressed by a pressure sensor array. A key feature of MI is "knowledge-based imaging". To produce a 3D image, the computer uses both the measured parameters of an individual examined object and a general database on anatomy and pathology of the object.[59]

Tactile imaging is a medical imaging modality that translates the sense of touch into a digital image. The tactile image is a function of $p\ (x, y, z)$, where p is the pressure on the soft tissue surface under applied deformation and x, y, and z are the coordinates where p was measured. The tactile image is a pressure map on which the direction of tissue deformation is specified.[63]

Functional tactile imaging translates muscle activity into dynamic pressure pattern $p\ (x, y, t)$ for an area of interest, where t is time and x, y are coordinates where the pressure P was measured. It may include: (1) Muscle voluntary contraction, (2)

involuntary reflex contraction, (3) involuntary relaxation, and (4) specific maneuvers.[61]

Biomechanical mapping = Tactile imaging + Functional tactile imaging.[64]

A tactile imaging probe has a pressure sensor array mounted on its face that acts similarly to human fingers during a clinical examination, deforming the soft tissue and detecting the resulting changes in the pressure pattern on the surface. The sensor head is moved against or over the surface of the tissue to be studied, and the pressure response is measured at multiple locations along the tissue. The results are used to generate images that show pressure distribution over the area of the tissue under study. The tactile image $p\ (x, y, z)$ reveals tissue or organ anatomy and elasticity distribution.[61]

History

Throughout the years several mechanical and tactile imaging systems have been developed for prostate, breast, muscle, and other soft tissues. The prostate mechanical imager (PMI) was designed to assist in diagnosis of prostate pathologies. The PMI system works through use of a transrectal probe with two pressure sensing arrays to acquire data from rectal wall and anus, and a 3D orientation sensor. The device aims to provide a more accurate and sensitive method for detection of prostate abnormalities as opposed to digital rectal examination (DRE).[65] Figure 1 presents mechanical images of the prostate. The left panel presents 2D cross-sectional mechanical images for the 3D prostate image presented on the right panel. These images clearly demonstrate the prostate abnormality with a nodule in the left lobe and prostate asymmetry. In the clinical study of 168 patients the PMI was able to create full 3D mechanical images of the prostate in 84% of patients while demonstrating a higher sensitivity than DRE for the biopsy detected nodules.[66]

In the application of MI technology for breast, the breast mechanical imager (BMI) was designed to image breast tissue and assist in the diagnosis of benign versus cancerous lesions.[67] The BMI had 2D pressure array with 192 pressure sensors. An examination procedure and algorithms to provide assessment of breast lesion features such as hardness related parameters, mobility, and shape have been developed. Figure 2 presents an example of the MI of a breast lesion. A statistical Bayesian classifier was constructed to distinguish between benign and malignant lesions by utilizing all the listed features as the input. Clinical results for 179 cases collected at four different clinical sites, established a reliable image formation of breast tissue abnormalities and calculation of lesion features. The tactile imaging demonstrated increased hardness and strain hardening as well as decreased mobility and longer boundary length in comparison with benign lesions for the histologically confirmed malignant breast lesions. Statistical analysis of differentiation capability for 147 benign and 32 malignant lesions revealed an average sensitivity of 91% and specificity of 87%. The area under the receiver operating characteristic curve characterizing benign and malignant lesion discrimination is 86% with the confidence interval ranging from 80 to 91%, with a significance level of

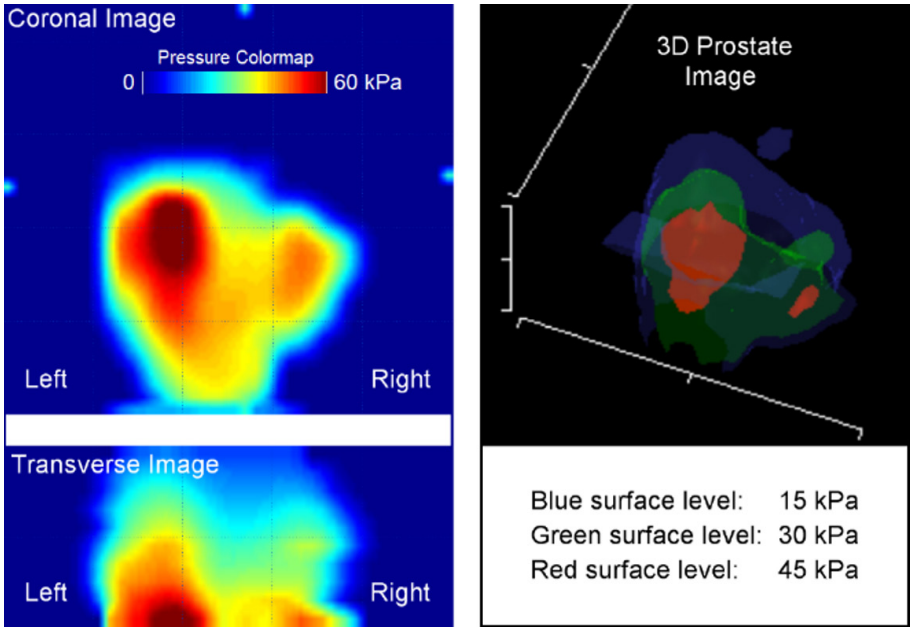

Figure 1. Prostate mechanical imaging for a 62 y.o. patient. Left panel - 2D orthogonal cross-sections of prostate, coronal (upper left) and transversal (lower left) tactile images; right panel - 3D reconstruction of the prostate with three iso-surfaces of pressure (see text)

p=0.0001.[68] We hypothesized that the BMI has the potential to be used as a cost-effective device for cancer diagnostics that could reduce the benign biopsy rate, serve as an adjunct to mammography and to be utilized as a screening device for breast cancer detection.

For validation of the MI devices, the tissue elastometer was designed to measure stress-strain relationship for soft tissue and to calculate its Young's modulus in the range of 10-400 kPa. In the testing of the excised tissue samples the repeatability of elasticity measurements was demonstrated in the range of 8-14%.[69]

Quantification of the mechanical properties of muscle is of a significant clinical interest. Local changes in the mechanical properties of muscle are often associated with clinical symptoms. In particular, myofascial trigger points (MTrPs) are a very common, yet poorly understood and overlooked cause of non-articular musculoskeletal pain. MTrPs are localized, stiff, hyperirritable tender nodules, palpated in taut bands of skeletal muscle. Objective validated measures of the mechanical properties of MTrPs could potentially be a clinical outcome measure. Ultrasound shear wave elastography and tactile imaging as complementary objective methods to assess the mechanical properties of MTrPs were explored on 50 subjects (27 healthy controls and 23 with symptomatic chronic neck pain and active MTrPs). The upper trapezius muscles in these subjects were imaged using shear wave elastography using an external vibration source to measure shear wave speed and dispersion in tissue, and tactile imaging using an array of pressure sensors creating a 3D reconstruction of mechanical structures in tissue. It was found that symptomatic muscle tissue in subjects with neck pain is mechanically more heterogeneous and stiffer compared to normal muscle in control subjects.[70]

Changes in the elasticity of the vaginal walls, connective support tissues, and muscles are thought to be significant factors in the development of POP. It poses two questions specific to the biomechanical properties of pelvic support tissues: how does tissue elasticity affect the development of POP and how can functional elasticity be maintained through reconstructive surgery? A first prototype of vaginal tactile imaging probe for visualization and assessment of elastic properties of pelvic floor tissues was comprised of 120 sensors array for 2D pressure response pattern and a tilt sensor (Figure 3). We assumed that the slope of a peak pressure value related to specified zone inside a tactile image versus total applied force to the probe head

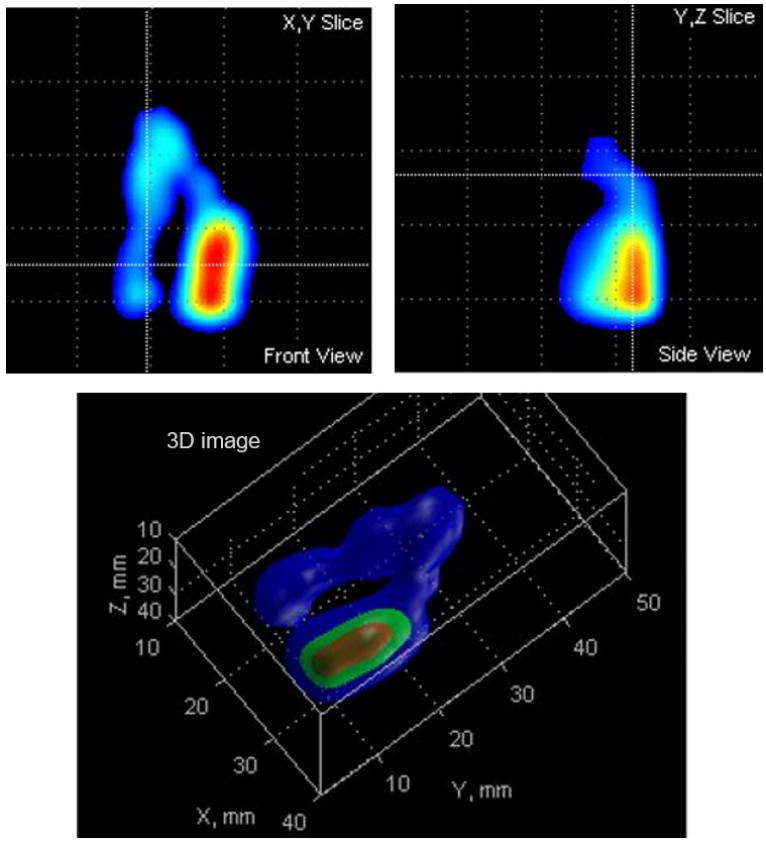

Figure 2. Mechanical imaging of breast lesion for a 45 y.o. patient. Upper panels - 2D orthogonal cross-sections of the lesion, coronal (left) and sagittal (right) mechanical images; lower panel - 3D mechanical image of the lesion

(scanhead) characterizes relative elasticity of a hard inclusion placed inside soft tissue against which the scanhead has been pressed. The probe was used in a pilot clinical study with 13 patients and demonstrated that vaginal walls increased rigidity due to implanted mesh grafts following reconstructive pelvic surgery and showed potential for prolapse characterization.[60]

The purpose of the next study was to assess the clinical suitability of 3D vaginal tactile imaging and tissue elasticity quantification under normal and prolapse conditions. The updated tactile imaging device included a vaginal probe with a 6D (three coordinates and 3 angles) electro-magnetic motion tracking system. The pressure sensor array comprised 128 capacitive pressure sensors.[20] Three orthogonal projections of the 3D vaginal pressure integrated response (tactile image) with probe location are observed by the operator in real time. The examination procedure with the vaginal probe included multiple compressions of the vaginal walls and composition of a circumferential 3D vaginal tactile image.[61] Figure 4 presents examples of examination results for normal and prolapse conditions. Specifically, Figure 4A shows transverse and sagittal cross-sections of the 3D vaginal tactile image for a 63 y.o. patient with normal pelvic floor anatomy on manual palpation during physical examination. Figure 4B shows transverse and sagittal planes of 3D vaginal tactile image received with VTI for a 77 y.o. patient with Stage III prolapse in the anterior and upper half of the posterior compartment that recurred less than a year from a vaginal hysterectomy and anterior repair. Study with 31 subjects demonstrated significant differences in anterior and posterior vaginal tissue elasticity with POP development stage ($p<0.0001$). The most affected locations were the mid and apical aspects of the anterior vaginal walls, where elasticity is decreasing up to 340% from normal to POP stage III. The lesser affected was the mid-posterior part where elasticity decreased up to 220%, the apical side walls of the vagina (decrease of approximately 100%), and the mid side walls of the vagina where we did not detect statistically significant tissue elasticity decrease. That means the horizontal (anterior, posterior) support structures weaken the most under POP conditions. This approach also allowed anatomical characterization of POP development. Specifically, we found that the anterior/posterior spacing increases for the apical part of vagina from 18±6 mm under normal conditions to 32±12 mm under POP stage III. The comfort level of VTI examination was found very close to manual palpation by 77% of patients.[61]

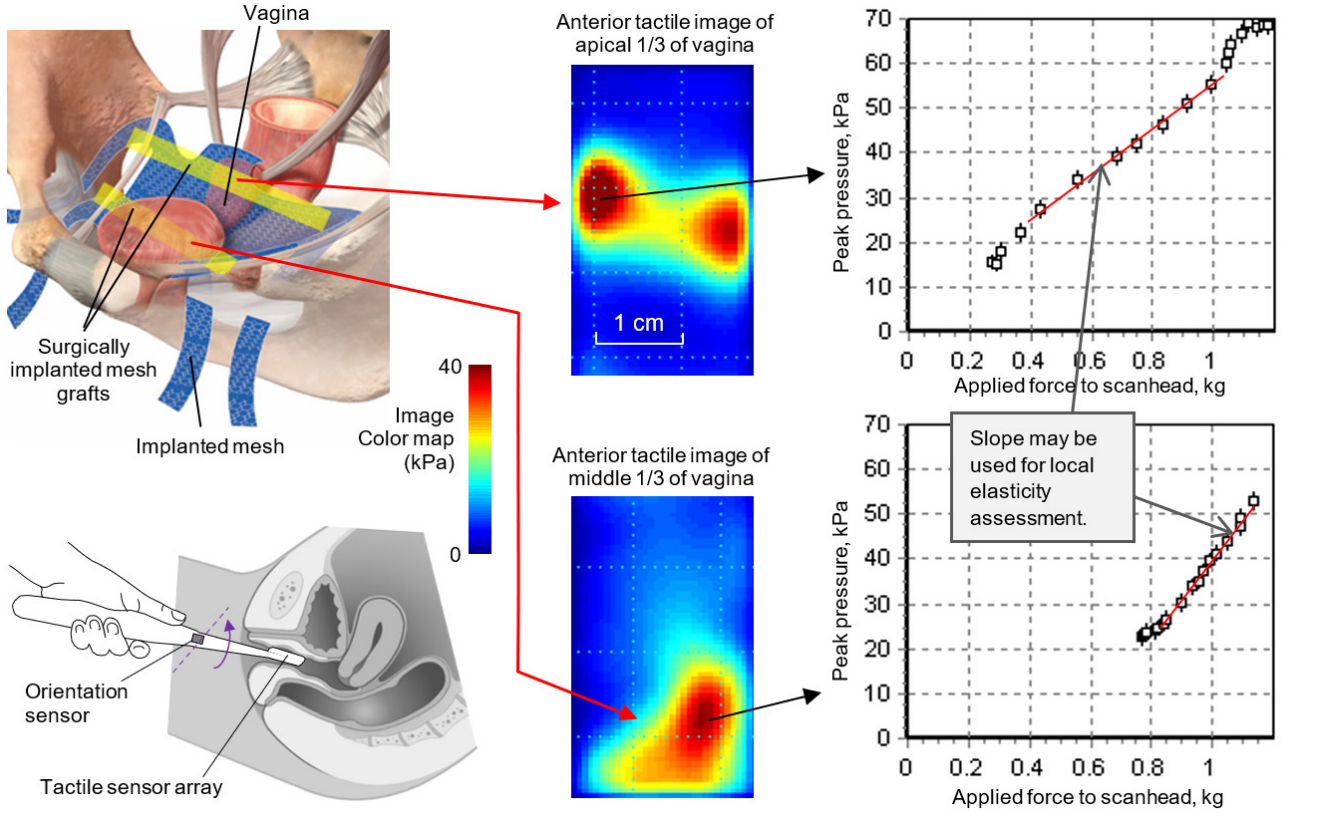

Figure 3. Tactile imaging of anterior and posterior vaginal walls. The diagrams on the left showcase the mesh graft implementation and below that shows a patient examination with the vaginal tactile imaging probe. This approach provides visualization and quantitative elasticity evaluation (see right graphs) at pelvic locations where these mesh grafts were placed (see two tactile images in the middle of the figure) [adapted from (60) with permission]

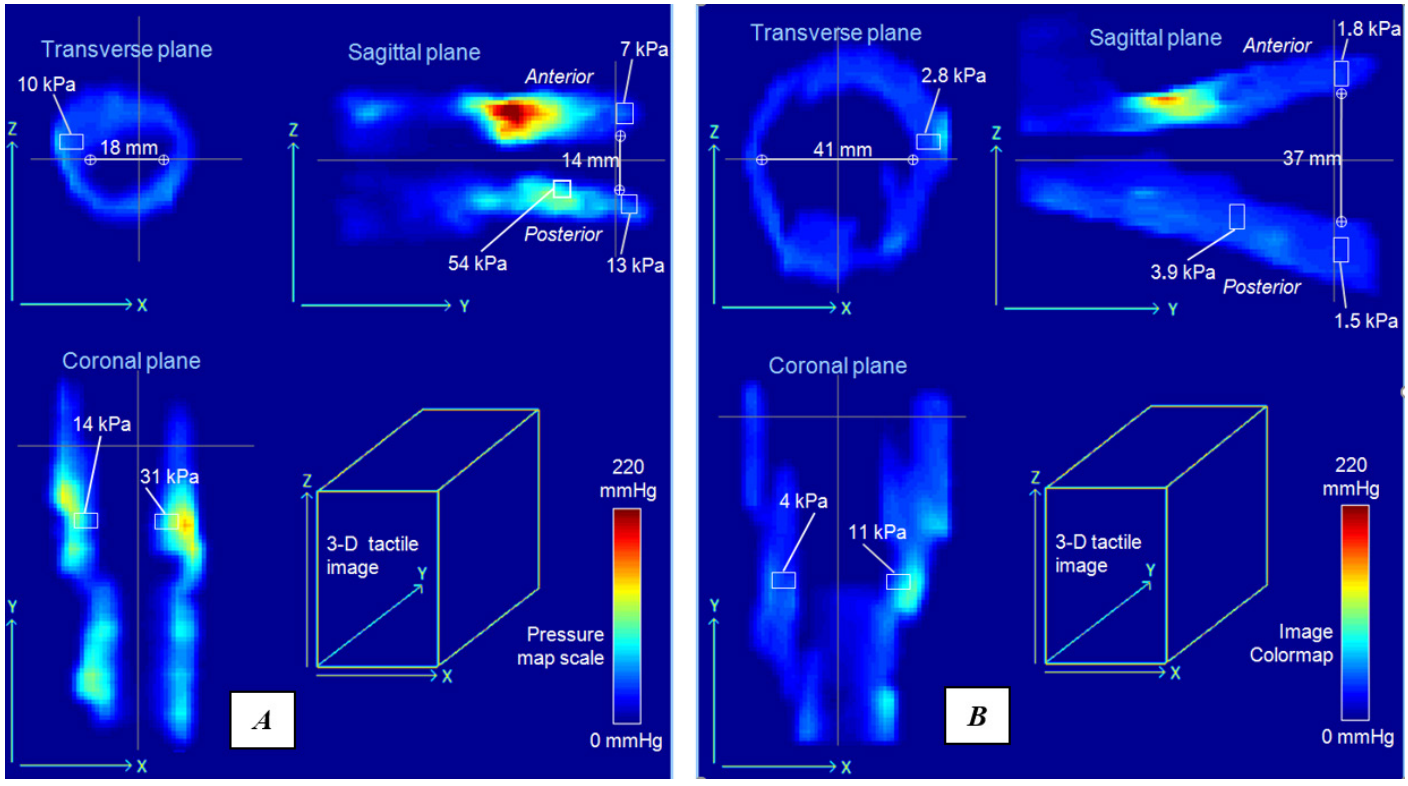

Figure 4. Cross-sections of 3D vaginal tactile images received with the vaginal tactile imaging device equipped with six-degrees-of-freedom motion tracking of the probe. The Y-axis represents distance along the vagina. Tactile images on the left are a patient with normal pelvic floor conditions (A) and tactile images on the right are of Stage III prolapse (B). Young's modulus (kPa) for vaginal tissue was calculated for areas specified by a rectangle [adapted from (61) with permission]

Vaginal Tactile Imager (VTI)

The VTI comprises a vaginal probe with 96 pressure (tactile) sensors, an orientation sensor, temperature sensors, micro-heating elements, and an electronic board (see Figure 5A). The pressure sensors provide pressure patterns (25 frames per second) from contact with the vaginal walls during the examination. The 3D accelerometer is used to measure the rotation and elevational angles of the probe. Probe positional information is combined with the pressure patterns from the tactile sensors to accurately track the location of the probe in the female pelvic floor during the examination. The temperature control system (micro-heating elements and temperature sensors) preheats the probe body including the tactile sensors to a temperature of 36 °C before the examination begins. The temperature stability of the probe increases accuracy of the tactile sensors and improves patient comfort. During the patient examination procedure, data are sampled from the probe sensors and displayed on the VTI computer display in real time. The calibration chamber is used to calibrate the tactile sensors in the vaginal probe by applying air pressures in the range from 0 to 40 kPa. The tactile sensors are calibrated every time before the patient examination relative to two independent highly accurate air pressure transducers. A lubricating jelly is used for patient comfort and to provide reproducible boundary/contact conditions with deformed vaginal tissue.

The pressure sensors sensitivity, defined as an average noise level, was found of about 50 Pa with dynamic response 40 ms and a measuring range up to 100 kPa. The spatial resolution of 1.0 mm along the VTI probe is achieved by a real-time pressure and positioning data processing.

Intra- and inter-observer agreements were evaluated in the subset of 12 subjects that have been enrolled into a larger observational case-controlled study (NCT02294383 at ClinicalTrials.gov).[71] Two measurements of the full set of VTI parameters (markers) were obtained by two observers. Agreements within and between observers for VTI parameters were analyzed using 95% prediction intervals, Bland-Altman plot with 95% limits of agreement, and the intraclass correlation coefficient (ICC).[72,73] All twelve subjects were successfully scanned with the VTI four times; two scans were completed by each of two operators. Mean patient age was 39.0 years (range 26 to 60), pelvic floor conditions were from normal (10 subjects) to Stage I/II POP (one subject with Stage 1 and one subject with Stage II prolapse), and mean parity of 1.2 (range 0 to 2). The data set with 1920 VTI measurement

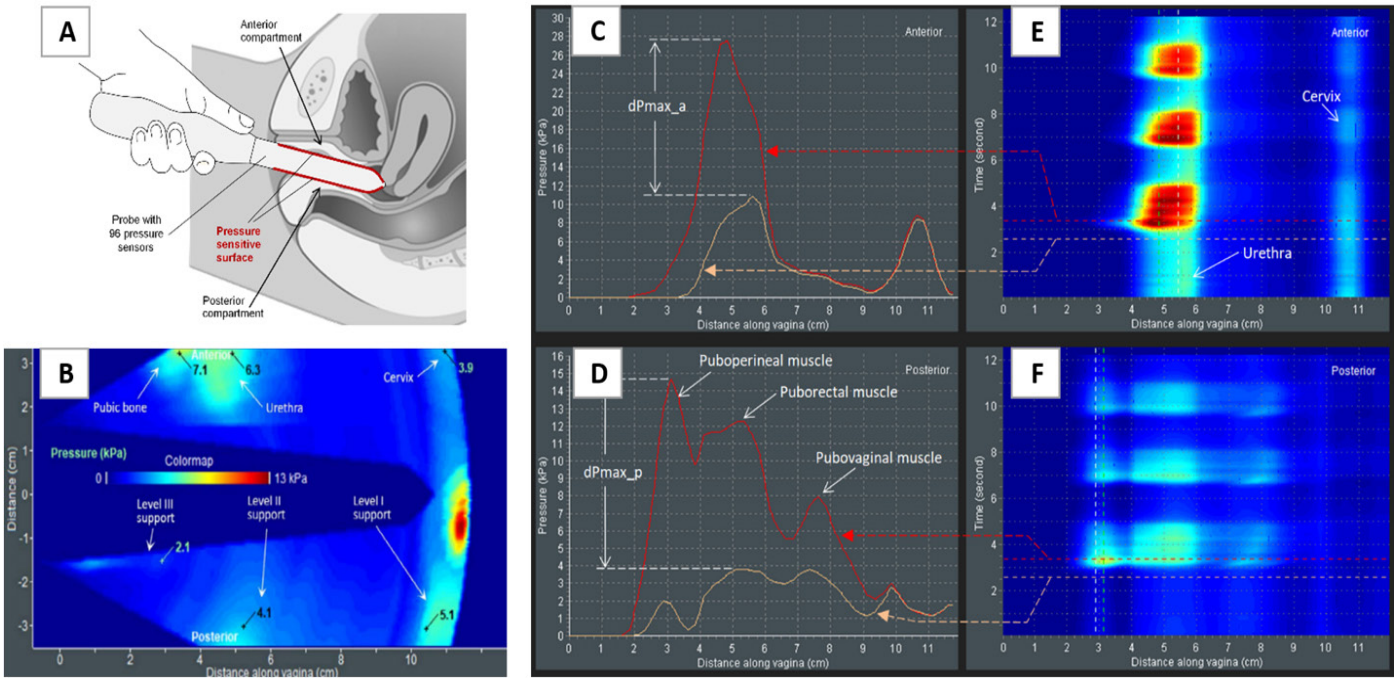

Figure 5. The vaginal tactile imaging probe with orientation sensor positioning during pelvic examination (A). Tactile imaging of anterior and posterior compartment at probe elevation relative to the hymen (B). Anterior (C) and posterior (D) pressure distribution along the vagina at pelvic muscle contraction. Dynamic pressure patterns along anterior (E) and posterior (F) compartments during pelvic muscle contraction

records (12 subjects x 10 parameters x 4 locations x 4 VTI scans) was analyzed. Intra-observer ICC was found in the range from 0.80 (Test 8: Reflex contraction at cough) to 0.92 (Test 3: Probe rotation) with average value of 0.87. Inter-observer ICCs were found in the range from 0.73 (Test 2: Probe elevation and Test 8: Reflex pelvic muscle contraction at cough) to 0.92 (Test 3: Probe rotation) with average value of 0.82. Intra-observer ICC was found in the range from 0.80 (Test 8: Reflex pelvic muscle contraction at cough) to 0.92 (Test 3: Probe rotation) with average value of 0.87 for all 10 parameters. Intra-observer limits of agreement were in the range from ±11.3% (Test 1: Probe insertion) to ±19.0% (Test 8: Reflex pelvic muscle contraction) with average value of ±15.1%. Inter-observer limits of agreement were in the range from ±12.0% (Test 5: Voluntary pelvic muscle contraction) to ±26.7% (Test 2: Probe elevation) with average value of ±18.4%. Based on these results the conclusion was made that there is reasonable intra- and inter-observer reproducibility for VTI measurements, though improved inter-observer reproducibility can be reached by operator training and consistency in VTI examination technique.[71]

The VTI examination procedure consists of eight tests: 1) Probe insertion, 2) elevation, 3) rotation, and 4) Valsalva maneuver, 5) voluntary muscle contraction, 6) voluntary muscle contraction (left versus right side), 7) involuntary relaxation, and 8) reflex muscle contraction (cough). Tests 1-5 and 7-8 provide data for anterior/posterior compartments; test 6 provides data for left/right sides. The probe's maneuvers in tests 1-3 accumulate multiple pressure patterns from the tissue surface to compose an integrated tactile image corresponding to each test for the investigated area using the image composition algorithms.[61] Tests 1 and 3 provide data for assessment of the vaginal tissue elasticity, test 2 provide parameters to characterize the pelvic support strength. Test 4-8 provide the dynamic pressure patterns for functional characterization. The VTI examination with all tests 1-8 completed takes 3-5 minutes. Figure 5 illustrates the probe positioning and examples of an acquired tactile images for the selected tests. Figure 5B shows acquired tactile images for anterior and posterior vaginal compartments for test 2 (probe elevation). The vaginal probe elevation acquires pressure feedback from the pelvic floor structures at about 15-40 mm depth under significant tissue deformation (up to 45 mm) for the anterior and posterior vaginal compartments. The VTI probe include an orientation sensor to measure an elevation angle, such that the pressure feedback acquired by pressure sensor arrays from the contact with the vaginal walls can be mapped along the elevation angle. The up and down elevation of the vaginal probe is usually completed relative to the hymen. In the anterior compartment, from left to right, tactile responses from the pelvic bone (pubic symphysis), the urethra, and the cervix may be observed. In the posterior compartment, from left to

right, tactile responses from Level III support, Level II support, and Level I support may be seen. Level III support includes perineum and puborectal muscle, Level II support includes puboanal and pubovaginal muscles, and Level I support includes iliococcygeal muscle, levator plate, cardinal and uterosacral ligaments.[17] Figure 5C illustrates the test 5 approach for VTI capturing parameters at voluntary muscles contractions. Three contractive peaks are observed in the posterior compartment which are described as originating from puboperineal, puborectal, and pubovaginal muscles. The contractive changes for these 3 posterior peaks have different value and separated along the vagina for the subject.

Comfort level: Based on the recorded feedback, subjects found on average the VTI procedure more or at least as comfortable as manual palpation. Specifically, 54% classified the VTI examination as more comfortable, 36% as the same, and 10% as less comfortable than manual palpation.[63]

Indications for use: The VTI was cleared by the FDA for the following indication "The VTI obtains a high-resolution mapping of pressures and assesses the strength of pelvic floor muscles within the vagina. It is used in a medical setting to acquire the pressures and store the corresponding data. It also provides visualization, analysis tools and information. The real time data as well the analysis information can then be viewed with an intention of assisting in the diagnosis and evaluation. The device is intended for use by physicians, surgeons and medically trained personnel".[74]

It is important to note that the VTI is not a diagnostic device; it is not intended to be used to diagnose any specific diseased conditions, such as POP or UI, on the binary basis as present versus absent. It is an imaging device and the image interpretation has to be completed by a clinician taking into account knowledge of general and functional pelvic anatomy, and their clinical experience and skills. The Integral Theory developed by Petros[22] may be used for identification of the pelvic floor structures contributing into the tactile images and dynamic pressure patterns acquired with the VTI.

VTI Clinical Applications

The VTI was uniquely designed to collect measurements for biomechanical characterization of the female pelvic floor. It is capable of quantifying muscle function, support strength, and tissue elasticity. This gives the device value in determining the inciting event for pelvic floor disease conditions. It was shown that with the VTI, a Biomechanical paradigm could achieve a baseline to assist in diagnosing POP conditions or estimate the risk factor for future POP.[14,61,75] Through this paradigm the pelvic floor conditions can be characterized by 52 VTI parameters derived from eight different tests (as previously described). This large body of measurements could be used to evaluate individual variations as well as identify specific potential markers that characterize tissue properties and muscle function in patients' diseased conditions that are accompanied by changes in mechanical properties and, often, physiologic manifestations. For a female patient that presents with complaints of increasing vaginal pressure, discomfort, backache, and bulging exacerbated by lifting and straining, the physician can perform transvaginal biomechanical mapping with the VTI probe to define the pelvic defects and to use this information to determine the best course of treatment. The procedure images are visualized in real time on a display to provide feedback to an operator, then used to produce an examination report in a form of a computer file and hard-copy record, so that the physician can review and interpret the results, dictate a report, and discuss the results with the patient. Clinical disorders that can benefit from the VTI to help optimize and monitor treatment include POP, stress UI, tissue atrophy, and others where the pelvic diseased conditions are accompanied by significant changes (100-500%) of pelvic tissue biomechanical properties and functions. The proposed approach also may help further differentiate the types of pelvic floor conditions, their underlying severity, and understand how to tailor treatments for the individual patient in the most effective manner.

Factors that expand on the biomechanical paradigm of the female pelvic floor include patient age, weight, height, and parity. The quantifiable impact of these factors was studied with the VTI.[76] Of the 52 VTI parameters, 12 had statistically significant correlation in patient age and 9 parameters were correlated with parity number. No parameter was found to have direct correlation with patient weight. Therefore, VTI measurements confirm generally observed correlation in age and parity with an increased risk of deteriorated biomechanical pelvic conditions. Future studies will be able to build on this information and give an increasingly more comprehensive understanding of the biomechanical condition that can be expected for a healthy patient.

A recent VTI study was designed to estimate the efficacy of different pelvic floor surgical procedures. Patients were recruited and examined prior to surgery and then four to six months after surgery. Seventy-eight cases with a total of 255 surgical procedures were included in reported data analysis.[77] The list of surgical procedures included sacral colpopexies, sacrospinous ligament suspensions, uterosacral ligament suspensions, illiococcygeal suspension, anterior and posterior colporrhaphies, enterocele repairs, perineorrhaphies, total and supracervical

hysterectomies, and midurethral sling. Results of the study demonstrated VTI documented biomechanical changes varied by procedure. The VTI parameters strongly correlated weak pelvic floor pre-surgery with positive POP surgery outcome of improved biomechanical properties. However, the data indicated that strong biomechanical pre-operative pelvic conditions may lead to negative changes after the surgery. Authors concluded that (1) POP surgery, in general, improves the biomechanical conditions and integrity of the weak pelvic floor, (2) the proposed biomechanical parameters can predict changes resulting from POP surgery.[77] This provides a promise of using the VTI to reduce the POP failure rates by preventing or delaying a surgery that would be ineffective for the individual. Additional studies and analysis could have the potential to inform surgeons on what procedure would work best on a case-by-case basis.

Another study was focused on hysterectomy patients and found a quantifiable change in key biomechanical properties of the tissues before and six months after surgery. Results showed mean tissue elasticity improvement due to the anatomical changes after hysterectomy, and mean urethral mobility decrease.[78]

In women with cervical cancer, treatment with radiation may cause changes in vaginal biomechanical properties, anatomy, and function. A study aimed to objectively assess effects of radiation therapy on vaginal elasticity, wall mobility, and contraction strength measured using the VTI, and to evaluate associations of these changes with sexual function. A total of 25 subjects with locally advanced cervical cancer were included in the final data analysis. Following radiation therapy, the mean scores for vaginal elasticity and vaginal tightening were significantly lower than at pre-treatment. Accompanied by the significant decreases in pelvic muscle mobility and pelvic muscle contraction strength. The conclusion was made that women with locally advanced cervical cancer who have been treated with radiation therapy exhibit persistent vaginal biomechanical changes that compromise sexual activity and result in considerable distress.[79] There are many other medical procedures that could get better efficacy and risk analysis with quantifiable biomechanical data from the VTI.

Recently, many clinics have been offering vaginal treatments using carbon dioxide lasers or radiofrequency devices. These are new procedures with relatively low efficacy data. The VTI is able to test the claims of these energy-based rejuvenation therapies. Three independent studies have been performed and found increases in both tissue elasticity and pelvic muscle strength.[80-82] All of these studies followed patients for under a year so it is hard to say what the long-term effects of vaginal rejuvenation would be. The overall population for these studies is still very low. Additional work would need to be done to fully validate such procedures.

The benefits of biomechanical data have been shown in multiple clinical studies but it became clear that 52 VTI parameters expressed in raw units might be difficult for interpretation in routine clinical practice. Ideally, for VTI measurements to be clinically useful, they should be presented in terms that are readily understandable by patients and clinicians as well as to be independent of the particular measurement device. that is why the biomechanical integrity score (BI-score) was introduced as a single parameter in the units of standard deviation to characterize the biomechanical status of the female pelvic floor.[83] The BI-score is built from five components derived from the VTI data: (1) Tissue elasticity, (2) pelvic support, (3) pelvic muscle contraction, (4) involuntary muscle relaxation, and (5) pelvic muscle mobility. The BI-score as well as all its five components were normalized using data from a clinical population with normal pelvic floor conditions. The BI-score for an individual is the deviation from the healthy population's average. Figure 6 shows the BI-score graph as it appears to the clinician. The graph is presented similarly to T-score for bone density, measured in units of standard deviation relative to the patient's age. To validate this approach, 253 subjects with normal and POP conditions were included in the multi-site observational, case-control study; 125 subjects had normal pelvic floor conditions and 128 subjects had POP stage II or higher. The *p*-value for the BI-score in POP population versus normal population was 4.3×10^{-31}. A reference BI-score curve against age for normal pelvic floor conditions was defined. Three colored backgrounds (normal, transition and diseased zones) have been suggested to be used in the presentation of the patient VTI examination results as shown in Figure 6. The POP diagnostic accuracy of the BI-score, calculated as an area under a receiver operating characteristics curve for the analyzed sample, was found as 89.7%.[84] The dependence of the BI-score on age for normal pelvic conditions is described as a second order curve (see blue line in Figure 6); its ± standard deviations are depicted by the dashed curves. It is clear that an age-adjusted BI-score can also be calculated relatively to the normal similar to the Z-score in the bone densitometry. As with bone density measurement, it is important to monitor patient progress with or without treatment. For this reason, it would be important to define the minimal clinically important difference in BI-score. The future research directions also may address (1) BI-score use for monitoring of a pelvic floor treatment outcome, (2) obtaining periodic BI-scores before a woman has symptoms, (3) recommendation for specific treatment based on the five components, (4) predictive capabilities of the BI-score for symptoms. The BI-score is currently validated for POP, but

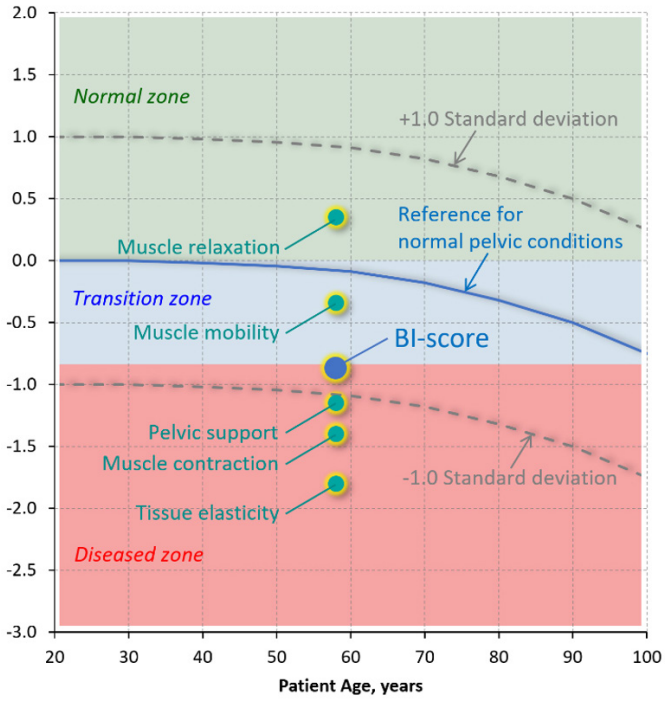

Figure 6. Biomechanical integrity score (BI-score) and its five components for a 58 y.o. patient acquired with the vaginal tactile imager (adapted from (83)]

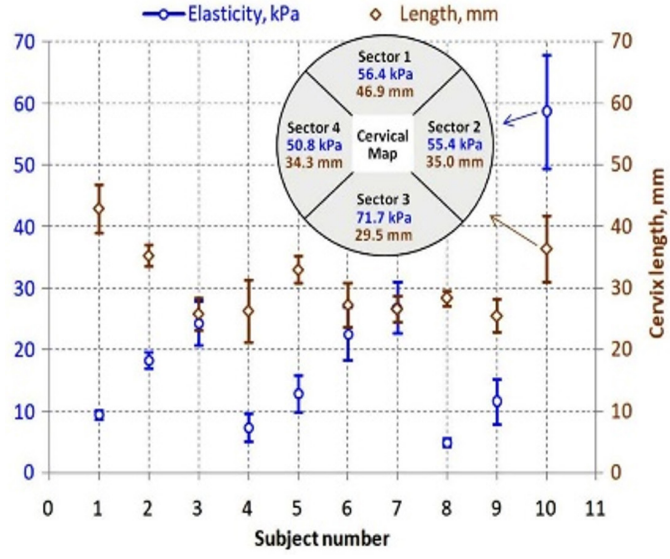

Figure 7. Cervical elasticity and length for 10 pregnant women measured with Cervix monitor and graphed by case. The circular cervical map shows averages values for the studied population in respective sector of the Cervix [adapted from (85)]

it can also be used for characterization of other pelvic diseased conditions which change the biomechanical components. This approach can be used in diagnosing and monitoring pelvic conditions as well as in selecting and evaluating treatment.

Future Directions

One of the greatest complications in infant and maternal health is a spontaneous preterm delivery. There are interventions that can reduce the harm of preterm birth however there is still no diagnostic tool to accurately forecast a preterm delivery. The Cervix monitor is a device that combines tactile and ultrasound technology to evaluate cervical depth and elasticity which may detect cervical conditions leading to spontaneous preterm delivery. The Cervix monitor probe has a single ultrasound transducer designed for cervical depth measurement. The probe then compresses the cervix, this compression creates a change in the ultrasound signal which is used to quantify cervical strain and tactile sensors to find an applied pressure to the cervical surface. With all that information the device can generate Young's modulus and depth for the patient's cervix. A pilot clinical study was designed to compare 10 non-pregnant women with 10 women 22-29 weeks pregnant.[85] It found that pregnancy decreased cervical elastic modulus from 54±17 kPa to 19.7±15.4 kPa. Additionally, pregnancy was correlated with a decrease in cervical length from 42±13 mm to 30.7±6.6 mm. The data in Figure 7 shows length and elasticity numbers for the 10 pregnant women in the study. It should be noted that soft tissue can vary drastically between individuals, however if the device tracks a single patient throughout pregnancy cervical effacement could be accurately measured and risk of preterm delivery may be identified and combined with the other important obstetrical markers. Extended clinical study with a larger sample size is on the way.

Another device designed to predict maternal birth trauma is the antepartum tactile monitor (ATM). A highly specialized probe with a double curve sensor array designed to simulate the shape of fetal head during delivery (see upper panel in Figure 8), sets ATM apart from the VTI in addition to other differences in technological as well as in clinical aspects. The ATM vaginal probe uses a six degrees-of-freedom electromagnetic motion tracking sensor to generate accurate positions and orientations in space of all 168 tactile sensors to form tactile images. Using the probes geometry and the tactile imaging information, the computer performs finite element modeling (FEM) to calculate Young's modulus of the tissues. Examination procedure was designed with the probe being inserted and contacting the critical locations along the birth canal to receive stress-strain data for structures behind the vaginal walls and estimate the critical measurements between opposite sides of the vagina. The probe is pressed and slides along the posterior vaginal wall until reaching the vaginal introitus. Then the probe is rotated and the same procedure is done on the anterior vaginal wall.

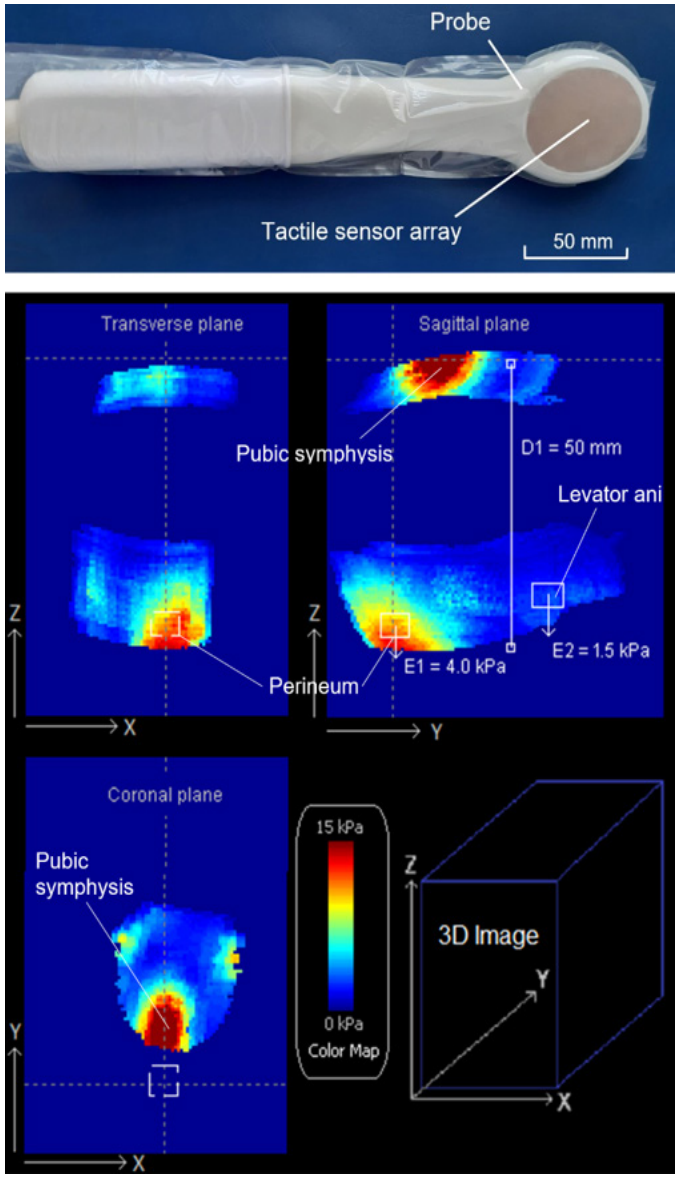

Figure 8. Top image shows the antepartum tactile monitor (ATM) probe, below is a screenshot from the ATM software interface showing tactile images in three orthogonal cross-sections with Y-axis representing distance along the vagina [adapted from (86)]

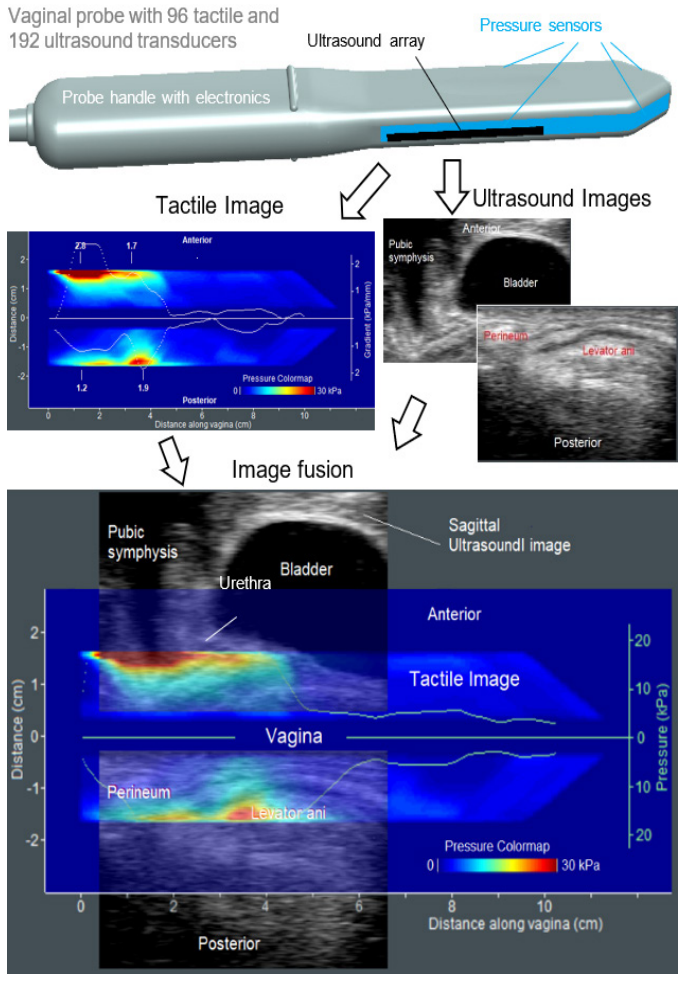

Figure 9. Tactile and ultrasound image fusion for test 1 (probe insertion) allows identification of pelvic anatomical landmarks and elasticity assessment for critical structures; 34 y.o. women with normal pelvic conditions [adapted from (88)]

This procedure forms tactile images of the perineum, levator ani, and pubic symphysis (see Figure 8). In a study of the ATM, 20 nulliparous women were successfully examined with real-time observation of the probe location, applied load to the vaginal walls, and 3D tactile image composition. Authors concluded that tactile imaging reproducibly characterized perineal elasticity and pubic bone-perineal critical distance.[87] The ATM requires further technological development and clinical validation.

Tactile (stress) and ultrasound (anatomy, strain) image fusion may furnish new insights into soft tissue characterization. A study was completed to explore imaging performance and clinical value of vaginal tactile and ultrasound image fusion for characterization of the female pelvic floor. A novel probe with 96 tactile and 192 ultrasound transducers was designed. Intravaginal tactile and ultrasound images were acquired for vaginal wall deformations at probe insertion, elevation, rotation, Valsalva maneuver, voluntary contractions, involuntary relaxation, and reflex pelvic muscle contractions. Biomechanical mapping included tactile/ultrasound imaging and functional imaging. Twenty women were successfully studied with the probe. Tactile and ultrasound images for tissues deformation as well as functional images were recorded. Tactile (stress) and ultrasound (strain) images create stress-strain maps for the tissues of interest in absolute scale. Functional images allowed identification of active pelvic structures and their biomechanical characterization (anatomical measurements, contractive mobility and strength). Fusion of

the modalities provides recognition and characterization of levator ani muscles (pubococcygeal, puborectal, iliococcygeal), perineum, urethral, and anorectal complexes critical in prolapse and/or incontinence development. Figure 9 presents an example of tactile ultrasound image fusion for yest 1 (probe insertion); identifying specific pelvic structures contributing to the tactile image composition (pubic symphysis, urethra in anterior and perineum, levator ani in posterior compartments). The pressure gradient distributions (kPa/mm) for vaginal wall deformation is orthogonal to vaginal canal direction (up and down) revealing elasticity distribution along the vagina. It has been concluded that vaginal tactile and ultrasound image fusion provides unique data for biomechanical characterization of the female pelvic floor.[88]

Further, the fusion of tactile and ultrasound techniques in one probe has fundamental importance, because these technologies are complementary to each other: Tactile images provide stress data and ultrasound images provide strain data as well as anatomy for the same tissue during its deformation. This approach might be used for the detection and characterization of endometriosis, adenomyosis, uterine fibroids and ovarian cancer; as well as breast cancer. Vaginal tactile ultrasound imaging may provide characterization of levator ani muscles (pubovaginal, puboanal, puborectal, iliococcygeal), perineum, urethra, and key ligaments (cardinal and uterosacral) critical in POP/UI development. Imaging of the anatomical and mechanical defects within the pelvic floor, provides anatomical and functional information necessary for a custom pessary design. The biomechanical data can be applied for computer simulation of surgical procedures and treatment effectiveness. Bringing novel biomechanical characterization for critical soft tissues/structures may provide extended scientific knowledge and improve clinical practice.

CONCLUSION

Obstetrics and gynecology are integral parts to the healthcare system and the continuation of a thriving population. While it is evident that diagnostics are progressing at a rapid pace it seems urogynecologists are relying on manual palpation and speculums for characterization and monitoring of the diseased conditions which effect millions of women. The new biomechanical paradigm for tissue/structure characterization may improve diagnostic accuracy of complex pelvic floor disorders and selection rate of optimal treatment. Biomechanical mapping of the female pelvic floor before surgery and probability assessment for success of specific surgical procedures and their combinations to recover healthy biomechanical status of the pelvic floor may change clinical practice.

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Platelet rich plasma (PRP) for vaginal tightening: A new approach

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ABSTRACT

Vaginal laxity is an anatomical deformation that can cause orgasmic dysfunction, decrease in self-esteem, worsen sexual life and quality of life in women. Although vaginal tightening has often been tried to be achieved by surgical methods, nowadays there is an increasing tendency to use non-surgical methods and to combine surgeries with non-surgical methods. These methods are non-invasive, safe, easy to apply and can be performed in private clinics as a daily outpatient procedure. A Their place in regenerative medicine is increasing day by day. Autologous platelet-rich plasma (PRP) has received more attention in cosmetic surgery, functional cosmetic genital surgery. PRP treatment stimulates neovascularization and collegen formation with the help of the growth factors that are secreted from the alfa granules of the platelets. It can be used in lichen sclerosis, vaginal atrophy, stress urinary incontinence, episiotomy scars, cervical ectopy and vaginal rejuvenation. We aimed to review the literature for PRP application in gynecology.

Keywords: Non-surgical gynecologic cosmetics; platelet-rich plasma; vaginal laxity; vaginal tightening

INTRODUCTION

Congenital differences such as labial hypertrophy, asymmetric labial growth; vaginal laxity due to obstetrical traumas, genetics, weight fluctuations; dyspareunia due to episiotomy scar, lichen sclerosis, vaginal atrophy following chemotherapy for breast cancer, genital urinary syndrome of menopause can lead to situations such as a decrease in self-esteem, sexual unsatisfaction, orgasmic dysfunction and decrease of quality of life.

Vaginal laxity as a part of natural process occuring with aging, chilbirth and menopause can cause decreased introital friction, diminished arousal and orgasmic dysfunction. It can also adversely effect women's sexual health and body image.[1] This has led clinicians to seek new, safe and effective surgical or non-surgical solutions to restore the function and form of the genital area.[2,3] Non-surgical approaches such as platelet-rich plasma (PRP), hyaluronic acid fillers, energy based devices and lipofilling

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are gaining popularity day by day due to their safe and effective outpatient application.[4]

A detailed electronic database (PubMed) search was performed for the review of studies involving PRP application. PRP, vaginal rejuvanation, vaginal laxity, vaginal tightening, female genital cosmetics were used as research terms.

PRP

It is reported in the literature that many different synthetic materials such as calcium hydroxyapatite cyristals, hyaluronic acid fillers, PRP are injected into the periurethral area and vaginal walls for the treatment of sexual issues and stress urinary incontinence.[5]

PRP is a novel autologous regenerative treatment method which gained popularity in the 1980s and 1990s and used almost in all fields of surgery such as orthopedics, dentistry, plastic surgery and gynecology to promote tissue healing and regenation.[6-8] It is considered to be safe, low-cost, simple, natural and minimally invasive method for vaginal rejuvation.

As the name suggests, platelet rich plasma contains a high percentage of platelets which is above that normally contained in whole blood. Autologous PRP is obtained by taking the patient's whole blood then centrifuged to remove red blood cells. Platelets have a capacity to supply and release essential growth factors and cytokines from their alpha granules to provide a regenerative stimulus that promotes repair in tissues and augments healing. It is a natural source of autologous growth factors.[9] It contains molecules that stimulate cell proliferation and cell differentiation such as transforming growth factor-β, insulin-like growth factor , vascular endothelial growth factor, epidermal growth factor and platelet derived growth factor (PDGF) (Table 1). These molecules play an important role in inflammation reduction, collagen III synthesis, angiogenesis stimulation and as a result in tissue regeneration. PDGF has been reported to stimulate cell proliferation and is involved in wound healing.[10] It is a mitogen for smooth muscle cells and fibroblasts. It plays role in angiogenesis, fibrous tissue formation and re-epithelialization which are phases of wound healing.[7]

Studies on the use of PRP in the literature are mainly urogynecology, and studies on its place in the use of vaginal laxity are limited.[5,11,12] Moreover, most of the existing studies consist of case reports and mostly PRP is combined with other minimally invasive techniques such as lipofilling or HA.[13,14] There are some studies investigating its effect on female sexual dysfunction and satisfaction.[5,15] However, it can be suggested that it may also be effective in the treatment of vaginal laxity due to its tissue regeneration feature.[16] It can also stimulate collagen synthesis, neo-vascularization which can also result in repair of vaginal laxity, improvement of sexual satisfaction and increase of quality of life.[7,10,15]

Table 1. Regenerative growth factors stored in platelet alpha granules and their functions[8,17]

Growth factor	Function
Transforming growth factor-β	Stimulates production of collagen type I and type III, angiogenesis,undifferentiated mesenchymal cell proliferation, endothelial chemotaxis, regulates mitogenic effects of othet growth factors
Insulin-like growth factor (1 and 2)	Regulates cell proliferation and differentiation, enhances bone formation, chemotactic for fibrobalsts and stimulates protein synthesis
Vascular endothelial growth factor	Increases angiogenesis and vessel permeability, stimulates mitogenesis for endothelial cells
Epidermal growth factor	Accelerates re-epitheliazation, increases tensile strength in wounds, regulates collagenase secretion, facilitates organization of granulation tissue
Platelet derived growth factor	Stimulates chemotaxis, cell proliferation, angiogenesis, regulates collagenase secretion and collagen synthesis
Fibroblast growth factor	Stimulates angiogenesis, promotes stem cell differentiation and cell proliferation
Connective tissue growth factor	Promotes angiogenesis, fibrosis and platelet adhesion
Platelet factor 4	Stimulates the initial influx of neutrophils into wounds
Interleukin 8	Recruirment of neutrophils and other immun cells to the site of infection, pro-inflammatory mediator

The Treatment Process

The limitation in PRP application is that the composition varies according to the device used, preparation method, preparation time, storage method and the composition of PRP varies from patient to patient.

There is no common consensus, no standard approach in terms of the anesthetic creams used, the areas where the injection is applied in the genital area, the frequency and doses of PRP injection for vaginal rejuvenation. Many clinicians have individualized their methods over time based on their own experience.

In order to induce release of a highly concentrated bolus of growth factors PRP preparations are activated. Up to 70% of

growth factor content from activated PRP can be released over 10 minutes. Roh et al.[18] demonstrated that PRP activated with a low-dose mixture of thrombin and calcium significantly increased growth factor release over 7 days compared with non-activated PRP. Although due to limited data there is no agreement on whether activation is beneficial or detrimental.

There are unique strategies used to put together the PRP, such as some practitioners use a centrifuge, whilst others use a double spin method. PRP cellular composition and biomolecular characteristics vary according to the preparation protocol.[19] In Giusti et al.'s [20] study, the optimal concentration for the stimulation of angiogenesis was $1.5x10^6$ PLT/µL and lower or higher concentrations displayed a lower angiogenic potential.

Although PRP application can be performed easily and without complications in clinical private practices with local anesthetic cream application, some patients may prefer the procedure to be performed under anesthesia in operating room due to their anxiety. In the literature, there are various cream mixtures with different contents and ratios used for topical anesthetic effect.

In Runels et al.'s[5] study bupivicaine, lidocaine and tetracaine cream compound with percent concentrations of 20/8/8 respectively was used. The cream was applied to the anterior vaginal wall and to the clitoris. PRP injection was performed 20 minutes after anesthetic application. Peripheral blood was centrifuged to yield 5 cc of PRP. They used either Regen® or TruPRP®. These both FDA approved systems use centrifugation to separate and concentrate PRP. They also added calcium chloride (0.5 mL) to the 5 mL of PRP isolate to activate the thrombin cascade. Injections were administered in less than 10 minutes to prevent platelet rich fibrin matrix from becoming too gelatinous for passing through a needle. Injections were given through a 27-gauge needle to the anterior vaginal wall into a space between vagina and urethra and into the clitoris. In this study, extreme sexual arousal was observed in 2 patients but these side effects only lasted 1 to 2 weeks and occurred in younger patients with minimal sexual dysfunction.

In Aguilar et al.'s [13] study, lipofilling and injection of combined PRP and HA was applied to a 39-year-old primiparous woman who referred for sexual dysfunction. They performed the procedure under general anesthesia. They used Regen®- BCT Cellular Matrix kit. The peripheral blood was withdrawn from the patient and collected into three single use sterile tubes (4 mL per tube). 4 mL of PRP-HA mixture (2 mL of PRP for 2 mL of HA) was prepared. The tubes were centrifuged at 1500 g for 5 min. Concomitantly the fat was harvested according Coleman's technique and was then centrifuged at 1500 g for 1 min. Then fat cells were injected in the posterior vaginal wall and the injection of the PRP-HA preparation in the perineal raphe, in the vestibular fossa and in the labius minus and majus. They reported that the total procedure took 30 min. They also reported that at 3-month follow-up the patient's symptoms improved significantly. She reported that her flatus incontinence disappeared completely.

In Kim et al.'s [14] study, PRP and lipofilling was applied to a 67-year-old patient for vaginal atrophy and lichen sclerosis. Autologous fat was harvested from the abdomen and mixed with autologous PRP. PRP was prepared by double-spin centrifugation using a SmartPreP® APC-30. A total of 36 cc of autologous fat was mixed 4 cc of autologous PRP. One month after injection her symptoms were resolved.

In another study, four sessions of PRP were administered to the anterior vaginal wall of 52 female patients with sexual dysfunction and orgasmic disorder.[15] A local anesthesia cream which contained lidocaine 2.5% and prilocaine 2.5% was applied around the clitoris and the vaginal lower one-third of the region half an hour before the procedure. The collected blood was centrifuged at 3200 rpm for eight minutes. Calcium chloride (0.5 mL) was used for activation. PRP of 4 cc was administered around the clitoris in the direction of clock positions of 12,3, 6 and 9, each with 1 cc, 2 cc subcutaneously; right/left of paraurethral vaginal wall. The administration was continued once every four weeks for four months. An increase in the satisfaction of the patients were observed in this study.

Contrary to what can be seen in calcium Hydroxyapatite Crystals or HA fillers in the literature, complications such as granuloma formation, infection or local tissue necrosis have not been reported if the procedure is performed by an expert clinician and if FDA-approved kits that are used for preparation of PRP.[5,21] Also there are no reports of allergic reaction due to PRP injection.

PRP application is not recommended in individuals who are taking antiplatelet therapy or who can not delay this treatment, and individuals using non-steroidal anti-inflammatory drugs (NSAIDs), reversible cyclo-oxygenase inhibitors, and anti-hyperglycemic pioglitazone, since these medications may significantly reduce the improvement potential of PRP treatment.[8] In addition to these, the use of systemic immunosuppressants such as glucocorticoids, blood dyscrasias and antibiotic use due to infection can be counted as medical contraindications. Being unable to tolerate injection therapies or afford to undergo a potential series of injections may be non-medical contraindications.

Patients should be informed that they may experience discomfort, swelling and redness in the injection areas after the procedure. These complaints often disappear within a few days. In addition, the information that they can easily return to their

daily routines after the procedure and that they will not need to rest can be given before the procedure. If only PRP application is performed as a rejuvantion procedure than sexual intercourse, heavy exercise and using tampon are not recommended for only 1 week after the procedure. Also they should avoid using NSAIDs for 2 to 6 weeks after the procedure. They can use acetaminophen as an alternative to NSAIDs as painkiller.

DISCUSSION

As stated in Shaw et al.'s [22] guideline no: 423, healthcare providers should educate women about female anatomy and anatomical variations. It is stated that most women who seek genital cosmetic surgery have normal genitalia, and up to 87% are reassured by counselling.[22] However, we can offer both surgical and non-surgical methods to the patient in cases such as vaginal laxity that can disrupt the person's sexual life and self-confidence.[1]

Although methods such as vaginoplasty, perineoplasty, colpoperineoplasty are preferred in vaginal tightening, non-surgical methods such as HA, PRP fillers, lipofilling and energy based devices have become more preferred among both patients and healthcare providers today.[4,23-25] Some frequent outcomes encompass enchancment in vaginal tightness, decreased stress urinary incontinence, and elevated sexual function.[13-15] These consequences may additionally be transient or permanent, relying on the method and the patient's recuperation process.

While PRP is used in many fields of medicine due to its positive effect on wound healing, its use in urogynecology and vaginal rejuvenation, either alone or in combination with methods such as HA and lipofilling, has begun to enter the literature.[5,6,9,11]

Its autologous nature, the low complication rate, ease of preparation and application, and outpatient applicability suggest that PRP application will increase its popularity in many areas of gynecology such as vaginal rejuvenation, urogynecology in the coming days. However, differences in preparation and application techniques, variability in cell numbers and the scarcity of studies in the literature indicate that our knowledge in this area is still limited and more prospective randomized studies are needed.[15,19]

CONCLUSION

PRP application in vaginal laxity and rejuvenation is a safe, simple and minimally invasive method, both alone and in combination with surgical approaches due to its accelerated wound healing effect. More prospective randomized studies are needed in gynecological practice in order to reach a consensus on the preparation and administration and the optimal cell amount.

ETHICS

Peer-review: Externally peer-reviewed.

Contributions

Concept: G.S., A.A.S.; Design: G.S., E.Ö., A.A.S.; Literature Search: E.Ö.; Writing: G.S., E.Ö.

DISCLOSURES

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