

# What Every Woman Should Know about Cervical Cancer

Nenad Markovic • Olivera Markovic

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 Springer

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## **To Our Family**

*In memory of our wonderful parents for raising us to search for truth, their magnificent devotion to the family and their love*

*Our dear children with love and hope they will continue our legacy*

## A Story about This Book and the Authors

During the 2006 Annual Meeting of the American Association for Cancer Research (AACR) in Washington DC, we had the pleasure to meet Dr. Cristina Alves dos Santos, Senior Publishing Editor, Cancer Research at Springer, NL. Discussing our work on cervical cancer screening which was presented at the meeting and how we came to our discovery, Dr. Dos Santos suggested that we consider submitting a manuscript to Springer for publishing.

In the beginning, we thought it would be interesting to write more about us, our work together as a husband-wife team, how we came to these discoveries and how we proceeded with translational research and brought them from an idea to products.

However, this idea, no matter how attractive it seemed, had to be replaced with the actuality of the momentum – the necessity to provide women with a reference book to help them better navigate among new dilemmas and multiple options that modern medicine was offering.

What happened between 2006 AACR Meeting and our decision to write the book *What Every Woman Should Know About Cervical Cancer*? In 2006, the FDA approved the first HPV vaccine (Gardasil by Merck) and raised everybody's hopes for successful prevention of cervical cancer. It turned the accent from cytological screening to HPV testing, and to the molecular testing – a logical extension to include detecting viral particles. These molecular biology-related ideas called for substantial increase of cervical cancer screening cost, and the funds-sensitive health insurance companies sounded alarm. The first signs of the worst solution appeared when Kaiser Permanente, accepting the new technology, recommended extending the periods between two cytological screenings for cervical cancer.

At that time, we were studying the relation between conventional Pap smear and the newly recommended liquid-based technologies in order to position our biomarker-based test to serve women's need best. One of the striking results from this study was the conclusion that the frequency of screening (annually) is probably better related to the success of Pap test (reduction of mortality from cervical cancer for 85% in the US), than the testing technology or false readings that has been a widely accepted argument against the Pap test. Recommending to extend the inter-screening periods was an alarming sign signaling to a danger that women could be again insufficiently protected against cervical cancer. More evidence-based information was needed to prevent an unwanted outcome.

We decided to use this opportunity and to write a book with emphasis on health education, a book that will synthesize the new achievements and will present them in the context of basic facts and prior advancements. Dr. Dos Santos liked this idea, and when she accepted the proposed synopsis and contents of the book, we started to work. This is how the book *What Every Woman Should Know About Cervical Cancer* was borne as an one-stop cervical cancer resource for women. Presenting medical concepts in plain terms with readily available advices, we thought, we could help women (1) to increase the awareness of risks and the availability of methods to prevent cervical cancer, (2) to educate them of available cancer control measures: how to detect early curable pre-cancerous disease and stop the cancer before it appears, and finally (3) to show them how to seek for appropriate help when cancer is diagnosed. This triad was intended to help women to promote their health, to ask educational questions from doctors and to participate actively in their diseases treatment, when needed.

Having experience with cancer patients and motivated by the current open forums, list serves and chats on the internet among women with pre-cancer and cancer, we decided to devote more space in this book for discussions on the emotional, humane side of the problem of how to cope with the disease (Chapter 3). Since many women are interested in complementary medicine, we have chosen to include some carefully selected topics (e.g. relaxation and stress release, eating for optimal health, etc.) Dr. Olivera Markovic, having experience as a university health professor and being acquainted with the needs of health instructors

and students complemented the text to make the book useful for an academic environment. Dr. Nenad Markovic, an experienced oncologist enriched the book with critical thinking on medical aspects of cervical cancer prevention (including HPV vaccination), control (past, current and new screening methods), diagnosis (colposcopy, biopsy, histology) and therapy (surgical, radiotherapy and chemotherapy), with emphasis on controversies and hopes created with the introduction of HPV vaccination. We hope these additions will be of benefit for medical personnel, students and doctors.

The anticipated story about the authors had to be limited to their joint but abbreviated biography. Drs. Olivera and Nenad Markovic are peers, collaborators and husband-wife lifetime partners. This was decided when they met in high school as best students in their generations, started and finished medical school on the same day in their home town, Skopje, Macedonia, former Yugoslavia. They were supported by their wonderful parents. Mr. Svetomir Markovic, Nenad's father who was a renowned educator, professor of mathematics and his mother Olga, who devoted her entire life to the family. Dr. Trajko Saljinski, Olivera's father was DVM and Ph.D. in veterinary microbiology, Senior Scientific State Counsel and Director of the State Institute of Microbiology. He inspired her to love science since she was a little girl spending lot of time with him in the laboratory. Her mother Mila, a talented vocal and instrumental artist and professor, ignited a love for music. Olivera was enrolled since age 6 in the school of music studying piano for 8 years.

After finishing their medical studies, Olivera and Nenad already married, planed together their further education and specializations (residency and fellowships). Nenad decided for clinical medicine and specialized internal medicine, hematology and oncology. Olivera decided for research and teaching and specialized medical biochemistry. At that time, they were immediately hired at the University Medical School in Skopje: Nenad at the University Clinic of Internal Medicine and Olivera at the Institute of Biochemistry, where they began academic career as assistant professors. Nenad had his residency in internal medicine at the University of Skopje, at the University in Belgrade and later at the University of Lund, GH in Malmo, Sweden. There, working with Prof. Dr. Jan Waldenstrom, he discovered his affection for studying cellular structures and their

functional meanings – a step that has influenced his further carrier. Olivera decided to postpone her specialization becoming a mother of their first child, Svetomir. She then completed the specialization in medical biochemistry at the University in Skopje and at the University in Belgrade. Soon after that their second child, daughter Mila was born.

At this time, Olivera was awarded the Fogarty International Research Fellowship at the National Institute of Health, Bethesda, Maryland. The family with two small children and a nanny arrived in Bethesda, Maryland. Olivera started her fellowship at the National Institute of Arthritis Metabolism and Digestive Diseases (NIAMDD) with Dr. N. Raphael Shulman as her mentor. Nenad soon was accepted as a clinical associate at the Leukemia Service, National Cancer Institute, to work with Dr. Edward Henderson.

Olivera started with her research on the maturation and differentiation of megakaryocytic-platelet blood lineage and discovered the importance of the change of the megakaryocytic acid phosphatase isoenzyme spectrum along the lineage maturation. This work was later published in *Blood* together with Dr. Shulman and attracted a lot of scientific interest. Nenad implemented his experience from Malmo, and was able to define several image analysis principles that are currently in use in digital image processing. It was an unforgettable time full of hard work, excitement and scientific achievements. NIH became a second home to Drs. Markovic. At that time, they both started their doctoral dissertations.

After returning to Yugoslavia they continued their graduate education working with Academic Professor Dr. Stanoje Stefanovic (Nenad) and Academic Professor Dr. Lubisa Rakic (Olivera). They both later defended their doctoral dissertations at the University in Belgrade. Nenad also completed the requirements for subspecialities in hematology and oncology. Olivera has already completed her specialization in medical biochemistry.

Soon, Nenad was awarded the NIH Fogarty International Research Fellowship at the National Cancer Institute and the whole family moved again to Bethesda. Olivera's mentor, Dr. Shulman, offered her a position Visiting Scientist to NIH. At NIH, Nenad and Olivera had the opportunity to work together on molecular imaging and quantitation of biologically active substances, primarily enzymes and their kinetics inside single cells. Together with their American colleagues



they pioneered in the application of image analysis in biomedicine. This was again a productive time full of hard work, discoveries and publications, but also an amazing time working in the unique atmosphere at NIH meeting new colleagues and friends.

After the second stay at NIH, Olivera and Nenad again returned to the former Yugoslavia to transfer their knowledge and experience in their home country. Nenad continued with his practice, introduced the first leukemia protocols in Yugoslavia, became Head and later Director of the University Clinic for Hematology at the University in Skopje.

Olivera developed a new clinical laboratory service at the University Children Hospital and became Chief of Clinical Laboratories.

They continued their collaboration with NIH through scientific projects and joint programs involving young people. Nenad became the President of the Association of Yugoslavian Oncologists. At this position, he organized National Congress with international participation, and coordinated efforts of multiple specialists who were involved in providing health care in the field of oncology to create a unique policy that was accepted at the Congress. Later, this policy became a Resolution for Management of Malignant Diseases declared by the Federal Assembly of Yugoslavia.

In the follow-up to this Resolution, Drs. Markovic moved to Belgrade and Novi Sad where Nenad started to work on the implementation of this Resolution. With the full support of Yugoslav Government, Nenad began developing a new cancer institute in Novi Sad, a copy of the NCI in Bethesda. This work was fully supported by NCI and the US Government who prepared the feasibility study for this development. As a part of the same concept, Olivera developed a new drug and diagnostic tests discovery and research laboratory in the University Clinical Center of the University of Belgrade. She was promoted Head of the Laboratory for Research and Development at the University Clinical Center in Belgrade.

They both advanced as university professors and continued their joint research, published numerous publications and participated as presenters, moderators and organizers on national and international scientific meetings and congresses. To fulfill the Resolution goals related to education, Nenad created the educational programs for undergraduate and graduate students which were adopted as the regular curriculum for medical studies in the School of Medicine, University of Novi Sad. Professor Dr. Nenad Markovic became the

first Chair of Oncology in the whole Yugoslavia. Unfortunately, this development was interrupted by the political disintegration of Yugoslavia (1990–1993) and Drs. Markovic returned to the US where they had established their second residency and where their children were studying.

Between 1983 and 1993, Drs. Markovic were working on both continents being invited as visiting professors at Penn State University, The University of Pennsylvania and Medical College of Pennsylvania (MCP). During that time, Dr. Nenad Markovic developed the first English Medical School at the University in Novi Sad. The Medical School was organized according to the curricula of MCP and the requirement of the ECFMG. The affiliation was built between the Belgrade and Novi Sad medical schools and MCP, with joint academic programs and exchange of students and faculties. The contribution provided by Dr. Walter Cohen, the President of MCP, the Dean Dr. Alton Sutnick and the Chairmen of the Department of Pharmacology Dr. Jay Roberts from US side was crucial for the success of this affiliation. The school is still active, but the affiliation with MCP stopped by the same reason as the program for developing national cancer center – political interests were stronger than the public needs for protection from cancer.

In the nineties the whole family moved to the US and continued their scientific and academic careers. Their son, Svetomir, finished medical school and graduate school at MCP and his residency in internal medicine and hematology/oncology at the Mayo Clinic, Rochester, MN. He continues his brilliant career at Mayo Clinic as a physician and researcher, partner and Associate Professor at Mayo Clinic. Their daughter Mila, a talented young lady graduated from business school and became a business expert in the health insurance industry. She is living with her family in Toronto, Canada. Following the tradition of her mother and grandmothers, Mila is also a devoted parent to our grandson Michael. We are very proud on our children.

Olivera and Nenad continued working together and returned to Washington Metro Area. Nenad joined the Food and Drug Administration and Olivera continued teaching at universities and colleges in the Metro Area (University of Maryland at College Park, American University, Georgetown University). Besides basic medical science courses (biology, human anatomy and physiology, biochemistry and pathophysiology), she also enjoyed teaching different health

courses (women's health, personal and community health, drug use and abuse and strategies in stress release). Dr. Olivera Markovic is still active professor.

In the late 1990s, Drs. Markovic became troubled by the reports of Pap test diagnostic failures, law suites that followed, laboratory liability, and decided to respond the call for improvement of Pap test technology issued by NIH, NCI Consensus Conference on Cervical Cancer in 1996. They recognized that in their research, they have discovered something that might be helpful to ameliorate this situation, and they decided to explore this option for the benefit of American women in a short term, and for the benefit of all women in the long term planning. This is how they began working systematically on the Cervical Acid Phosphatase (CAP). They found that this isoenzyme molecule is exclusively present in abnormal cervical pre-cancerous and cancerous cells and that normal cervical epithelial cells are entirely negative on Pap specimens. They succeeded to visualize this biomarker of cellular abnormality as an intracellular red insoluble deposit on the bluish Papanicolaou stained background. Making the abnormal cells more visible with the biomarker, they aimed to alleviate the disadvantage of Pap test related to the high percentage of false-negative results (because of missing abnormal cells). This is how Cervical Acid Phosphatase-Papanicolaou test, the CAP-PAP test, was borne and patented in the year 2000. In the meantime, Olivera decided to incorporate BioSciCon, Inc., the R&D biotech and consulting company, to proceed with this research. Nenad joined later.

The NIH recognized the potentials of the new test and supported BioSciCon with SBIR phase 1 and phase 2 grants. Again, with the support of NIH, their *alma mater*, they conducted a translational research on 2,000 patients from general population and women at high risk, and showed that that the MarkPap<sup>®</sup> test (trademark for CAP-PAP test) is more accurate, faster and less expensive. The test was given to a manufacturer to prepare a kit for in vitro diagnostic procedure, and the entire development is now awaiting the FDA approval for marketing in the US. BioSciCon, Inc. appeared at the NIH success stories page ([http://grants1.nih.gov/grants/funding/sbir\\_successes/155.htm](http://grants1.nih.gov/grants/funding/sbir_successes/155.htm)).

The new biomarker also opens a new prospective for telemedicine, MarkPap<sup>®</sup> Digital (future Tele Pap test). Using an easy-to-use MarkPap Kit, specimens can be processed in a small laboratory or

doctor's offices by a low-trained technician or a nurse. Since the abnormal cells are already marked red with the biomarker, the same person could see those cells in the microscope and immediately transmit their images to a laboratory with specialists for final evaluation. The result may be returned within hours. It means that the Pap test could be made available around the world bypassing the need for developing an expensive infrastructure. Drs. Markovic are currently working on the development of MarkPap® Digital.

There is one more important barrier for providing the Pap test globally and save women's lives. Women do not get screened not only because there is no Pap test accessible to them or they can not afford it. They may have other restrains, like cultural/religious traditions preventing them to visit gynecologist or they are simply afraid of pelvic exam and feel uncomfortable with it. In the US, there are currently 20 million women who know about Pap test, have this test available, but do not take it. For all of them and women around the world, our ultimate goal is to develop a self-sampling test, MarkPap® Self (future HomePap). It is the presence of the biomarker that opens this prospective, which has been impossible to accomplish until now. MarkPap Digital and MarkPap Self are expected to make the cervical cancer screening available to all women in the world. HPV vaccination and biomarker-based cytological cervical cancer screening, like MarkPap test, open realistic hopes for the eradication of cervical cancer in the 21st century.

In order to accomplish this last task in their life-time efforts, Dr. Olivera Markovic recently incorporated a non-profit organization, *The Global Academy for Women's Health, Inc.* ([www.GAWH@markpap.com](http://www.GAWH@markpap.com)). The Academy's mission is the advancement in education and science for women's health. The book *What Every Women Should Know About Cervical Cancer* is the first accomplishment of the Global Academy for Women's Health.

Drs. Markovic currently reside in Rockville, Maryland, USA, and continue with their research. Until today, they authored more than 200 publications including books, chapters in books, invited lectures, scientific publications and presentations, and patents. Their current activity is devoted to the research and development of their proprietary MarkPap technology, to writing and teaching and hoping that thousands of women around the world will benefit from their hard work and devotion. This will be their legacy.

Drs. Markovic's biographies could be found in several bibliographical records, e.g., *Marquis Who's Who in America*, *Who's Who in the World*, *Who's Who is Science and Engineering*, *Who's Who is Healthcare*, *Who's Who of American Women* and in *The International Bibliographical Centre, Cambridge, England*.

## Acknowledgments

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# Introduction

I am a medical doctor practicing internal medicine, hematology and oncology for more than 40 years, who has spent the recent 10 years in the field of cervical cancer because my wife, Dr. Olivera Markovic, has discovered that female cervical epithelium contains a bioactive protein (biomarker) which may lead and help them to conquer the fear from cervical cancer, and we together decided to devote our lives for bringing this biomarker to the benefit of all women.

During this period I've seen thousands of women coming to my office for help because of their concerns, fears, physical and psychological problems mostly related to cancer. Very early, I learned that the best way to deal with their problems is to hear the patient's complaints, to examine carefully and to teach them to understand the cause of their concerns and to help them deciding for the best treatment approach available. I also found how profound knowledge of human soul had Hippocrates of Kos (ca. 480–375 BC) who wrote, "In practicing his profession, a doctor can rarely cure, could improve the condition many times, but always must help those who ask for help."

Dr. Olivera Markovic is a medical doctor and a Ph.D. in biochemistry, who was practicing laboratory medicine, but has devoted the last two decades of her professional career to cancer research. She is also a lifetime educator teaching basic medical science, science and health related courses. During the recent years she has taught Women's Health and related courses at local colleges and universities in the Greater Washington Metro Area, where she learned how her students were unprepared for health challenges the adult life is bringing to them and learned how focused education could be both appreciative and successful.



When, because of the biomarker, we both dedicated our lives to women's health, we realized that the best way to accomplish new goals is to combine our research for bringing this biomarker to women's benefit with an appropriate education to help them understanding better the beauty and the risks of being a woman in the modern world, and the opportunities that all women have to protect themselves from cervical cancer. It is sad and unacceptable that millions of women, somebody's mothers, wives, sisters, daughters and granddaughters, still die from a preventable disease in the 21st century.

In the period when we were in dilemma what to do first, came 2006 Experimental Biology Meeting in Washington, DC where we met the Springer representative Ms. Christine Dos Santos who inspired us to write a book for Springer who will make it available to all women worldwide.

In the meantime, a major change in the strategy for prevention of cervical cancer occurred. Two pharmaceutical giants, Merck and GSK developed vaccines to immunize women against oncogenic strains of HPV. This achievement has raised hopes for more effective protection from cervical cancer. However, since the way to reach those hopes is long to go (decades), in the meantime, the newest strategy for cervical cancer prevention placed the emphasis on the motto "*no women should be left without cytological screening protection.*" Today, cytological screening for cervical cancer (Pap test) is not widely available. Only less than 10% of 1.7 billion women at risk have the opportunity to use this test in their developed and resourceful countries. The rest, most of them living in the low-resource developing countries have not this opportunity. World Health Organization and many governments all over the world are aware of the problems and are struggling to find ways to protect their female population with less expensive screening – but all efforts to replace the standard Pap test have not yet produced convincing results. The alternatives have not been shown to be at least not worse than the cytological testing.

Nevertheless, the news about vaccination has spread among women who are now increasingly asking whether, when and how to immunize themselves and their daughters against cervical cancer. Because of the inaccessibility of the best cytological test, the cost of vaccination, uncertainty of long term protection, ineffectiveness in all cancers and many still unresolved questions but great hopes, the public is alerted and

women are upset which way to go and how. This is perfect environment for a book like ours to bring a comprehensive insight to the problems as a basic knowledge and reference to web sites where women will be able to follow the updated information.

Finally, because of the grave prognosis of cervical cancer, if not detected and treated on time, and the opportunity for cure if detected, the early detection of cervical cancer or precancerosis, the Pap test, became one of the most regulated medical diagnostic tests in the history. In addition to Federal regulations (CLIA\*88 and amendments), many consensus conferences issued guidelines and guidance for medical procedures designed for early detection of cervical cancer and for products to be used in those procedures. All these documents are in public domain and are available for review on the Internet. As much as this “openness” is important for public education, reading this literature without prior knowledge could be a source of unnecessary misunderstanding, frustration and pain for readers. Our book will try to provide women with the basic knowledge, so they will read medical information with better understanding and, hopefully, will not regard the current medical strategies as biblical canons, but as temporary recommendations made by groups of experts based on their best knowledge and understanding. Emphasizing the transition of rules, we would like to open a window that neither bad diagnostic news are always bad as they look, nor the good news should always be accepted as a total relief – a certain degree of uncertainty must always be present and second opinion asked. This makes the difference between educated and non-educated patient, and could be of importance for women to better protect themselves in their life-long struggle to avoid cervical cancer or to cure it if the first goal was not achieved.

# Contents

<b>A Story about This Book and the Authors</b> . . . . .	vii
<b>Acknowledgments</b> . . . . .	xvii
<b>Introduction</b> . . . . .	xix
<b>1 The Female Reproductive System in Health and Disease</b> . . . . .	1
1.1 Basic Anatomy of the Female Reproductive System . . . . .	1
1.1.1 The Ovaries . . . . .	1
1.1.2 Fallopian Tubes . . . . .	4
1.1.3 The Uterus . . . . .	4
1.1.4 The Vagina . . . . .	5
1.1.5 The Vulva and the Perineum . . . . .	5
1.2 Basic Physiology of the Female Reproductive System . . . . .	6
1.2.1 Female Hormones . . . . .	6
1.2.2 The Menstrual Cycle . . . . .	6
1.2.3 Pregnancy . . . . .	8
1.2.4 Menopause . . . . .	9
1.3 An Overview of the Most Common Women's Diseases . . . . .	10
1.3.1 Menstrual Disorders . . . . .	10
1.3.2 Other Disorders . . . . .	12
1.3.3 Common Infections in Women . . . . .	13
1.3.4 Sexually Transmitted Diseases . . . . .	15
1.4 Tumors of the Female Genital System . . . . .	18
1.4.1 Benign Tumors . . . . .	19

- 1.4.2 Malignant Tumors Other than Cervical Cancer . . . . . 20
- 2 Cervical Cancer . . . . . 23**
  - 2.1 About Cervical Cancer and Pre-cancerosis in this Book . . . . . 23
    - 2.1.1 Introduction . . . . . 23
    - 2.1.2 Definition . . . . . 24
    - 2.1.3 Interpretation . . . . . 26
  - 2.2 Epidemiology of Cervical Cancer . . . . . 29
  - 2.3 Prevention and Control of Cervical Cancer . . . . . 41
    - 2.3.1 Risk Factors and Education to Reduce Their Influence. . . . . 43
    - 2.3.2 Cancer Control: Cervical Cancer/Pre-cancerosis Screening . . . . . 54
    - 2.3.3 Non Cytology-Based Cervical Cancer Screening . . . . . 82
    - 2.3.4 Management of Women When the Pap Test Result Returns . . . . . 88
    - 2.3.5 Biomarkers and Cervical Cancer . . . . . 96
    - 2.3.6 Human Papilloma Virus and Cervical Cancer . . 110
  - 2.4 Diagnosis and Treatment of Cervical Cancer . . . . . 119
    - 2.4.1 Diagnostic Methods . . . . . 120
    - 2.4.2 Staging System . . . . . 128
    - 2.4.3 Planning Therapy . . . . . 131
    - 2.4.4 Cervical Cancer Treatment . . . . . 132
  - 2.5 Prognosis of Cervical Cancer and How to Improve it. . . . . 140
- 3 Coping and Living with Cervical Cancer . . . . . 149**
  - 3.1 Coping . . . . . 149
    - 3.1.1 How to Cope When the Result is Abnormal Pap Test? . . . . . 150
    - 3.1.2 The Diagnosis is Cervical Cancer . . . . . 152
    - 3.1.3 Support from Caregivers and Close Family in Day-by-Day Coping with the Disease . . . . . 153
    - 3.1.4 Support of Extended Family and Friends . . . . . 156
    - 3.1.5 Support Groups . . . . . 156

- 3.2 Living with Cancer ..... 157
  - 3.2.1 Complementary and Alternative Medicine .... 158
  - 3.2.2 Holistic View of Health and Wellness ..... 160
  - 3.2.3 Which are Other Dimensions of Health Described as a Holistic Health Model? ..... 162
  - 3.2.4 How We can Achieve a Higher Level of Wellness Across all Dimensions of Health?..... 162
  - 3.2.5 Understanding the Mechanism of Stress ..... 166
  - 3.2.6 Stress Release Strategies ..... 168
  - 3.2.7 An Overview on Eating for Optimal Health in Cancer Prevention and Cervical Cancer .... 174
- 3.3 Stories from Real People ..... 175
- 3.4 Survey on What Women Think About Pap Test ..... 184
  - 3.4.1 Background ..... 184
  - 3.4.2 Identifying the Problem..... 185
  - 3.4.3 Addressing the Problem – Study ..... 185
  - 3.4.4 Study Results and Analysis ..... 186
  - 3.4.5 Interim Conclusion ..... 188
- 3.5 Where to Read More? ..... 189
  
- Literature Cited.** ..... 195
  
- Afterword.** ..... 207
  
- Index.** ..... 211



# Chapter 1

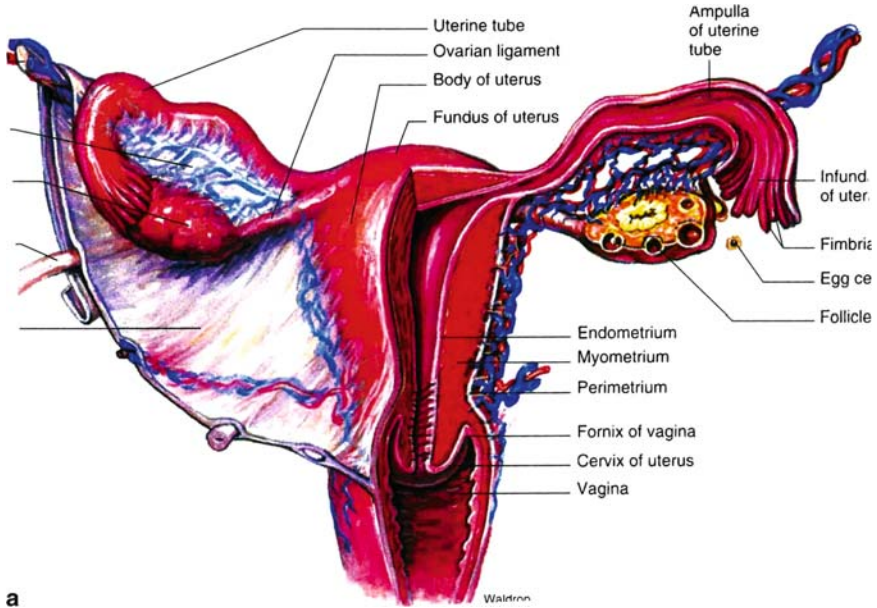
## The Female Reproductive System in Health and Disease

### 1.1 Basic Anatomy of the Female Reproductive System

*Introduction to the structure of individual organs of the female reproductive system: Ovaries (egg and ovulation, the corpus luteum). Fallopian tubes. Uterus: The upper part, the body of the uterus (corpus uteri. The lower, narrower part of the uterus is called cervix of the uterus (cervix uteri). Structure of the uterus. Vagina, vulva and perineum. Supportive tissues.*

#### 1.1.1 The Ovaries

The ovaries are two small oval, almond-shaped glands (4×2×1 cm) located in the pelvic portion of the abdomen on either side of the uterus (Figs. 1.1a and 1.1b). They are attached to the uterus and the body wall by ligaments. Ovaries produce eggs, e.g., “ova” and secrete female sexual hormones estrogen and progesterone. The ovaries are covered by a single layer of epithelial cells and beneath this layer ova are produced. The baby girl is born with about 60,000 ova. Each of these ova has the potential to mature, but only about 400 of them mature for fertilization during women lifetime. The process of maturation takes place in a small sack with cells filled with fluid that is called ovarian follicle. As the ovum matures, the cells in the follicular wall start secreting estrogen. When the ovum matured, the follicle ruptures and expels the ovum out of the follicle. This process is called ovulation. The ovum is then swept into the fallopian tube and starts its journey towards the uterus. After the ovum has been expelled, the remaining follicle is transformed into yellowish body called corpus luteum. This structure continues to secrete the hormone estrogen, and starts secreting the other



**a**



**b**

**Fig. 1.1** Anatomy of the female genital system: (with permission of the McGraw Hill Companies). **a.** Front view; **b.** Profile; **c.** External view; **d.** Female reproductive physiology: The cycle of ovulation and menstruation (Prints are from the book *Human Physiology* by Stuart Ira Fox, 6th edition, McGraw Hill Publisher, 1999)