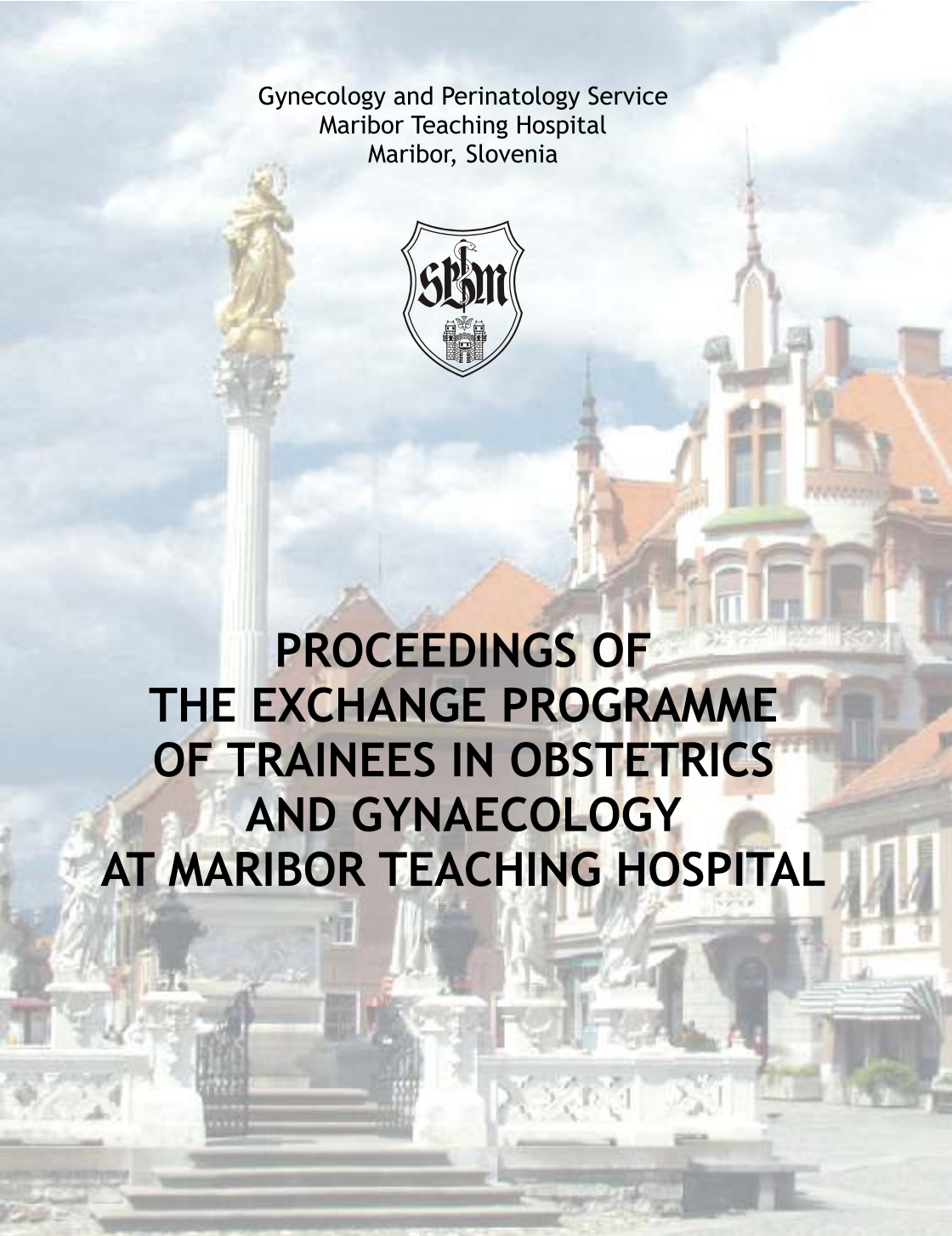
Gynecology and Perinatology Service
Maribor Teaching Hospital
Maribor, Slovenia



PROCEEDINGS OF THE EXCHANGE PROGRAMME OF TRAINEES IN OBSTETRICS AND GYNAECOLOGY AT MARIBOR TEACHING HOSPITAL

22 to 25 November 2004

EDITORIAL OFFICE
Maribor Teaching Hospital
Gynecology and Perinatology Service
Ljubljanska 5
2101 Maribor
Slovenia

Tel: +386 2 321 2178
Fax: +386 2 331 2393
E-mail: gin.perinat@sb-mb.si

AUTHORS

Darja Arko, MD, MSc, Department of Gynecologic Oncology and Breast Oncology, Maribor Teaching Hospital, Ljubljanska 5, Maribor, Slovenia

Robert Bali, MD, Department of Gynecologic Oncology and Breast Oncology, Maribor Teaching Hospital, Ljubljanska 5, Maribor, Slovenia

Prof. **Elko Borko**, MD, PhD, Department of General Gynecology and Gynecologic Urology, Maribor Teaching Hospital, Ljubljanska 5, Maribor, Slovenia

Silva Burja, MD, PhD, Department of Perinatology, Division of Neonatology, Maribor Teaching Hospital, Ljubljanska 5, Maribor, Slovenia

Ass. Prof. **Igor But**, MD, PhD, Department of General Gynecology and Gynecologic Urology, Maribor Teaching Hospital, Ljubljanska 5, Maribor, Slovenia

Ass. Prof. **Zlatka Rakovec Felser**, PhD, Gynecology and Perinatology Service Maribor, OPC for Psychooncology, Maribor Teaching Hospital, Ljubljanska 5, Maribor, Slovenia

Andreja Tekauc Golob, MD, Department of Perinatology, Division of Neonatology, Maribor Teaching Hospital, Ljubljanska 5, Maribor, Slovenia

Prof. **Borut Gorišek**, MD, PhD, Department of Gynecologic Oncology and Breast Oncology, Maribor Teaching Hospital, Ljubljanska 5, Maribor, Slovenia

Bojan Korpar, MD, Department of Perinatology, Division of Neonatology, Maribor Teaching Hospital, Ljubljanska 5, Maribor, Slovenia

Borut Kovačič, PhD, Department of Reproductive Medicine and Gynecologic Endocrinology, Maribor Teaching Hospital, Ljubljanska 5, Maribor, Slovenia

Marijan Lužnik, MD, MSc, Department of Perinatology, Maribor Teaching Hospital, Ljubljanska 5, Maribor, Slovenia

Ass. Prof. **Milan Reljič**, MD, PhD, Department of Reproductive Medicine and Gynecologic Endocrinology, Maribor Teaching Hospital, Ljubljanska 5, Maribor, Slovenia

Nina Čas Sikošek, MD, Department of Gynecologic Oncology and Breast Oncology, Maribor Teaching Hospital, Ljubljanska 5, Maribor, Slovenia

Ass. Prof. **Iztok Takač**, MD, PhD, Gynecology and Perinatology Service Maribor, Maribor Teaching Hospital, Ljubljanska 5, Maribor, Slovenia

Milena Treiber, MD, Department of Perinatology, Division of Neonatology, Maribor Teaching Hospital, Ljubljanska 5, Maribor, Slovenia

Prof. **Veljko Vlaisavljević**, MD, PhD, Department of Reproductive Medicine and Gynecologic Endocrinology, Maribor Teaching Hospital, Ljubljanska 5, Maribor, Slovenia

Prof. **Nadja Kokalj Vokač,** PhD, Gynecology and Perinatology Service Maribor, Laboratory of Medical Genetics, Maribor Teaching Hospital, Ljubljanska 5, Maribor, Slovenia

Jože Žolger, MD, Department of Perinatology, Division of Neonatology, Maribor Teaching Hospital, Ljubljanska 5, Maribor, Slovenia

CONTENTS

THE MARIBOR GYNECOLOGY AND PERINATOLOGY SERVICE – INTRODUCTION

Iztok Takač

ABSTRACT

On September 10, 2003, the Gynecology and Perinatology Service of General Hospital Maribor received the Certificate of the Accreditation of Training from the European Board and College of Obstetrics and Gynaecology (EBCOG). This sign of honor and responsibility was the result of a process starting a long time ago. The staff of the Gynecology and Perinatology Service struggled for many years to reach the point where such a professional, educational and research potential was achieved that it could be offered to trainees in obstetrics and gynecology as a part of their educational program.
Besides being an honor, the appointment for hosting a group of trainees in obstetrics and gynecology from different European countries at our institution also implies the responsibility for further improvement of the training program.

Key words: Gynecology and Perinatology Service, organization

INTRODUCTION

The Department of Gynecology and Perinatology was founded in 1928 within General Hospital Maribor which was, with its almost 2000 hospital beds, already the largest general hospital in former Yugoslavia.
According to the July 2003 Job Systemization Act of General Hospital Maribor, the Gynecology and Perinatology Service consists of:

- The Service Management
- Common Activities of the Service
  - Administration
  - ICU
  - OP Theaters
  - Outpatient Clinics
  - Primary Gynecologic Care Clinic
  - Breast Disease Center
  - Laboratory of Cytodiagnostics
  - Laboratory of Medical Genetics
- Department of General Gynecology and Gynecologic Urology
- Department of Reproductive Medicine and Gynecologic Endocrinology
- Laboratory of Reproductive Biology
- Department of Gynecologic Oncology and Breast Oncology
- Department of Perinatology
  Division of Neonatology

ORGANIZATIONAL STRUCTURE

1. Management of the Gynecology and Perinatology Service

1. Head: Ass.Prof. Iztok Takač, M.D., Ph.D.
2. Head Nurse: Danijela Pušnik
3. Secretary: Andreja Šlag

2. Common Activities of the Service

Administration: 16 clerks
ICU: 8 beds, 7 nurses
OP Theaters: 6 OP rooms, 11 OP nurses
Outpatient Clinics for US Diagnostics: 3 every day

Primary Gynecologic Care Clinics: 3 physicians, 6 nurses

OPC for Psychooncology
Ass.Prof. Zlatka Rakovec Felser, Ph.D.

Laboratory of Medical Genetics
Head: Prof. Nadja Kokalj Vokač, Ph.D.

Laboratory of Cytodiagnostics
Head: Kristina Kramberger Gornik, M.D.

3. Department of General Gynecology and Gynecologic Urology
Head: Ass. Prof. Igor But, M.D., Ph.D.
5 physicians
9 nurses

Capacity: 35 beds

Outpatient Clinics:
Day Clinics
Cabinet for Urogynecology

4. Department of Gynecologic Oncology and Breast Oncology
Head: Darja Arko, M.D., M.Sc.
10 physicians
11 nurses
Capacity: 36 beds

Outpatient Clinics:

Breast Disease Center
OPC for Colposcopy
OPC for Gynecologic Oncology
OPC for Breast Oncology
OPC for Psychooncology
OPC for Chemotherapy

5. Department of Reproductive Medicine and Gynecologic Endocrinology
Head: Prof. Veljko Vlaisavljević. M.D., Ph.D.
6 physicians
5 nurses

Capacity: 15 beds

Outpatient Clinics:

OPC for Female Infertility
OPC for Andrology
OPC for Assisted Reproduction
OPC for US Diagnostics

Facilities:
IVF laboratory
Andrologic Laboratory

6. Department of Perinatology
Head: Marijan Lužnik, M.D., M.Sc.
9 physicians
41 nurses

Capacity: 56 beds

Delivery Rooms
ICU for Parturient and Pregnant Women

Outpatient Clinics:

OPC for High-Risk Pregnancy
OPC for Cardiotocographic Monitoring of Pregnancy
OPC for US Diagnostics
OPC for Initial Examinations and Consultations
OPC for Genetic Counseling
School for Expectant Parents

5.1. Division of Neonatology
Head: Silva Burja, M.D., Ph.D.
5 physicians
18 nurses

Facilities: 38 beds (10 beds for ill neonates)

Unit for Healthy Neonates (daytime rooming-in, night station)
ICU for Neonates

Outpatient Clinics:

OPC for High-Risk Neonates
OPC for US Examination of Neonates
OPC for Neonates from discharge to one month

WORK LOAD

In 2003, the Gynecology and Perinatology Service had a capacity of 142 beds divided between four departments.
The total staff number was 210, among them 36 physicians, 9 biologists, 4 graduate chemical engineers, one psychologist, 36 graduate nurses, 87 nurses and 4 laboratory technicians.
In 2003 we had 10269 hospitalized patients. Among them 3888 were treated at day clinics. There were 1940 deliveries with 2002 births at the Department of Obstetrics. In that year we performed 4513 minor and 2187 major surgical procedures.
There were also 34796 performed outpatient obstetric and gynecologic examinations.
During the year 2003, 11 trainees were rotating among the different departments of the Gynecology and Perinatology Service.

TRAINING IN OBSTETRICS AND GYNECOLOGY

The plan for the rotation of physicians specializing in obstetrics and gynecology is defined by the Medical Chamber of the Republic of Slovenia. We keep strictly to the plan representing the minimum duration of specialization.
The specialization program foresees a two-months training period in radiotherapy at the Ljubljana Institute of Oncology and a 3-months period at the Ljubljana Gynecology Clinic.
The mentor's maximum supervision is ensured particularly in the OP and delivery room while certain phases of diagnostic and therapeutic work with outpatients is carried out by the resident gradually (in accordance with knowledge verified by colloquia), under the indirect supervision of the mentor.
Resident physicians are included in outpatient and hospital work, antenatal care, work in the delivery rooms as well as after delivery.
Each resident has a booklet to register each individual segment of specialist work performed. The resident must also collect the documentation regarding the entire specter of gynecologic and obstetric surgical activities.

GENERAL VIEWPOINTS OF TRAINING

The aim of specialization

Specialization in gynecology and obstetrics is a teaching and educational process in which the resident physician acquires such theoretic and practical knowledge from the field of gynecology and obstetrics that he/she is capable of independent care of most patients with acute and chronic gynecologic diseases. "Care" involves diagnosis, treatment and prophylaxis of female reproductive organ diseases and the study of factors affecting reproductive health. Specialization in obstetrics and gynecology includes the following: management, treatment of normal and pathologic pregnancy and delivery as well as treatment in the field of gynecologic urology and oncology, perinatology and reproductive medicine. Within the specialization the trainee also acquires the necessary amount of knowledge in the field of urology, abdominal surgery, pathomorphology, neonatology and outpatient method of work.

Specialization duration and structure

The specialization in obstetrics and gynecology lasts at least 5 years and includes the fields of gynecology, perinatology and human reproduction.

The specialization program

GYNECOLOGY	
General gynecology	4 months
Gynecologic oncology (with breast oncology)	4 months
Gynecologic urology	2 months
Emergency gynecology (inflammatory processes)	3 months
Child gynecology	1 month
Total	**14 months**
OBSTERICS	
Following of normal and pathologic pregnancy (OPC and hospital)	6 months
Delivery room	6 months

Total	**12 months**
REPRODUCTION	
Hospital Dept. of Reprod. Med.	3 months
IVF - ET program	2 months
Gynec. endocrinology	2 months
Family planning and birth control	2 months
Andrology	1 month
Total	**10 months**
Work at the OPC for women (includes family planning and birth control)	2 months
Psychosomatics in gyn&obst	1 month
Diagnosis of pathologic processes in the breast	2 months
Total	**5 months**
Abdominal surgery	7.5 months
Urology	2 months
Neonatology	1 month
Pathology	1 month
Oncology	2 months
Anesthesia	1 month
Human genetics	1 month
Ultrasound	3 months
Transfusiology	0.5 month (14 days)
Total	**19 months**
Total	**60 months**

Termination of specialization

The chief mentor establishes the specialization is terminated after verifying the adequacy of its duration, the fulfillment of conditions prescribed for the acquiring of knowledge, the number of interventions performed and successfully passed prescribed colloquia. The specialization is concluded by the specialist examination.

Verification of knowledge

Each resident has his own resident's booklet and a diary for recording of all performed interventions and first surgical assistances as well as his professional, educational and research contributions.
To ascertain a suitable quality of the specialization process, the candidate's acquired knowledge and his capacity is verified by constant monitoring and periodic verification - colloquia. The grading of knowledge is done by colloquium directly after the termination of work within each individual training unit. Separately and in official form, the resident must present his knowledge publicly at least once a year. The form of this presentation is determined either by the chief or by the direct mentor, i.e.:

* Presentation of patient analysis or individual clinical case report,
* Preparation of and presiding over a clinical or clinicopathological conference.

The condition for the continuation of specialization is the successful passing of colloquia and a satisfactory evaluation by the chief mentor every year.
Apart from the fulfillment of general conditions, prior to sitting for the specialist exam the resident physician must write and publish his specialist thesis. The specialist thesis treats an urgent problem in gynecology, perinatology or reproduction. The theme is chosen by the mentor.
The specialist thesis should be written in article form.

Catalogue of Required Procedures at the Dept. of General Gynecology and Gynecologic Urology

Diagnostic Procedures	
Colposcopy	100
Hysteroscopy	15
Laparoscopy	15
Gynecologic Operations	
Minor endoscopic op. (laparoscopic and hysteroscopic)	10
Hysterectomy:	
Abdominal	20
Vaginal	5
Urogyn. operation for reconstruction of pelvic floor	5
Diagnostic and therapeutic abrasion	100

Catalogue of Required Procedures at the Dept. of Gynecologic Oncology and Breast Oncology

Minor endoscopic operations	10
Voiding punctures of abdominal and thoracic cavity	10
Aspiration puncture with thin needle for CIT	30
Breast surgery	20
(Tumorectomy, quadrantectomy, mastectomy with evacuation of axilla)	20
Assisting	
Radical hysterectomy sec. Wertheim Meigs	5
Radical hysterectomy sec. Wertheim	10
Radical vulvectomy	3
Cytoreductive op. in ovarial carcinoma	5
Operation for breast cancer	20
Cooperation	
Chemotherapy for ovarian cancer	20
Chemotherapy for breast cancer	20
Chemotherapy for other gyn. malignancy	5

Catalogue of Required Procedures at the Dept. of Reproductive Medicine and Gynecologic Endocrinology

Diagnostic Procedures	
Diagnostic hysteroscopy	25
Diagnostic laparoscopy	20
Obtaining of cervical mucus and microscopic investigation techniques	20
Echographic investigation during first weeks of pregnancy	20
Hysterosalpingography	20
Folliculometry of ovulation induction with clomiphene	20
Folliculometry of ovulation induction with HMG	20
Echographic visualization of cavum and myometrium	20
Echographic investigation with abdominal probe	20
Operations	
Intrauterine insemination	20
Transvaginal puncture of ovary	20
Lysis adhesionum	5
Neotubostomy	5
Embryotransfer	5
Ablation of endometrium	5
Laparoscopic surgery for ectopic pregnancy	10

Catalogue of Required Procedures at the Dept. of Perinatology

US investigations (early pregnancy, morphology /under supervision/, following of fetal growth)	200
Suturing of episiotomies	100
Vaginal guiding of delivery in breech presentation	10
Vacuum extraction or forceps	10
Cesarean section	40
First assistance in cesarean section	20
pH-metry	20
Placenta separation	5
Uterine exploration	5

CONCLUSIONS

The Maribor Gynecology and Perinatology Service provides a wide spectrum of professional, educational and research work, which is also permanently used in the training program of trainees in obstetrics and gynecology. We have a solid staff platform and are quite well equipped with various sophisticated technologies necessary for professional and research work. Currently we are involved in several international research projects. On Sept. 10, 2003, our Service was accredited by the European Board and College of Obstetrics and Gynaecology as a European Training Center in Obstetrics and Gynecology for a period of five years. Consequently, trainees in obstetrics and gynecology from different European countries are most welcome to come to our institution and profit from Maribor's experience.

References

1. Strokovno poročilo bolnišnice 2003. Splošna bolnišnica Maribor, 2003.

THE GYNECOLOGY AND PERINATOLOGY SERVICE AT MARIBOR GENERAL HOSPITAL - HISTORIC OVERVIEW

Elko Borko

ABSTRACT

The article gives a description of the development of Maribor General Hospital (MGH) and its gynecologic part from the year 1234 - when Wolfram, the first known medical worker was active in Maribor - and up to the year 2000.

The development and progress of the Department of Obstetrics and Gynecology in the last decade is very impressive. A number of new activities were initiated, new diagnostic and therapeutic procedures were introduced.

Maribor is the second largest town in Slovenia and an important regional center. It is the industrial, cultural, academic and traffic center of northeastern Slovenia. It also has an interesting medical history. The name Marburg (Maribor) was first mentioned in a document dated 1164, in 1254 it was first mentioned as a town. The first known medical worker in Maribor was the surgeon Wolfram (Wolframus chirurgus) who worked in the town around 1234. The beginnings of our MGH stretch back to 1348. In that year two wealthy citizens, Matevž and his wife Katarina, founded a town hospice. It was not a hospital, but rather a shelter for the aged. Actual hospitals were in convents or monasteries (the Minorite monastery in Maribor was first mentioned in 1270), or they were temporary hospitals, intended for the treatment of wounded soldiers only. Such was the situation in Maribor when the Turkish sultan Suleiman II attacked with 100 000 soldiers in 1532.

An important milestone in the development of obstetrics, and of medicine in general, was the 18th century. In 1753 schools for midwives were opened in Ljubljana and Klagenfurt, some years later

in Graz (1776) and in Trieste (1815). The courses were in the Slovene language. In 1782 the first Slovene medical textbook was published in Ljubljana. In 1788 two other textbooks followed. These books played a vital role in improving both the theoretical and the practical aspects of midwifery and providing the foundation for Slovene gynecologic terminology. In 1840 the Graz obstetrician and midwifery teacher Kömm published his textbook, the "Book on Labor Assistance for Female Labor Assistants in the Countryside". It was written in Slovene. In 1799 a town hospital was established in Maribor, only six years after the one in Graz. It was situated close by the hospice on the site of today's Slomškov trg post office building. Initially it only had eight beds. Beside the sick, disabled and incurable patients were also admitted, so it was not actually a real hospital at that time. In 1843, the Maribor town hospital got a trained nursing staff: three Sisters of Charity who took over the care of the patients. At the same time the incurable patients were separated from the rest, so that the town hospital became an actual hospital with 40 beds in 1847. As a consequence of the construction of the Vienna-Trieste railway in 1846, the population of Maribor began to grow rapidly. Therefore the town hospital became too small and the town authorities bought the Prosenjak family villa in the Magdalena suburb, where the hospital was moved in October 1855.

In the first year after its relocation, the town hospital offered treatment to 470 patients. It had only two physicians, four Sisters of Charity, a hired man and a maid. In 1857 Maribor town hospital obtained the status of a public institution and received the title of General Hospital. Between 1864 and 1865, an additional tract including the mortuary was constructed as well as a barrack for patients with infectious diseases.

In 1872 the number of beds was 65 and the Internal (medical) and External (surgical) Departments were formed. Between 1879 and 1897, Maribor General Hospital (MGH) bought some neighboring plots of land and the Internal (medical) Department was built. The External Department was also located in the same building, admitting particularly surgical and gynecological patients. In 1896 the MGH had 200 beds. Between 1899 and 1903, the construction of a new Surgical Department, isolation ward, a new building for the kitchen, nutrition and maintenance services and a new mortuary was

carried out. The building of the former hospital was reconstructed for the management. In 1903 MGH had only five physicians on duty and this number remained almost unchanged till the end of WW I in 1918. In 1919, at the beginning of new pre-April Yugoslavia, several Slovene physicians came to MGH, and four new departments were formed: the Internal Department with isolation rooms, its Head was Dr. Ivan Matko, the Surgical Department headed by Dr. Mirko Černič, the Ophtalmo-Laryngeal Department headed by Dr. Janko Dernovšek, and the Dermato-Venereal Department headed by Dr. Hugon Robič. In 1919 the number of beds at MGH was 410. As soon as the financial conditions were settled, the expansion of MGH began. In 1927, the Maribor Antitubercular League pulmonary unit was founded at the Internal Department. In the same year the Institute of Radiology began its work. Its director was Dr. Benjamin Ipavec, gynecologist by profession and Wertheim's former assistant.

After many years of unsuccessful attempts, the Department of Obstetrics and Gynecology (OBG) was established in the former sanatorium at Vinarska Road in 1928. Its Head was Dr. Josip Benčan. The total number of beds at the new department was 22, with time increasing to 50. In 1928, the total number of beds at MGH was 485. Finally in 1929 MGH became a county hospital and several new wards were added: a new building for infectious diseases (1929), the post-mortem room (1930), and a dispensary clinic (1932). In 1933 the Medical Library including a reading room was opened. At this time the MGH had 565 beds. As the lack of beds increased, MGH began to build the new so-called black building. It was not finished before 1943, when the OBG as well as the ENT (Ear-Nose-Throat) and Ophthalmology Departments moved in.

1941 saw the beginning of the German occupation. Overnight MGH became a German institution. The Nazi invaders arrested many Slovene physicians, most of them were deported to Serbia, Croatia or Germany. The Resistance Movement was active in the hospital as well. The remaining nationally minded Slovene physicians and staff gathered medical supplies to secretly treat the members of the Resistance and the partisans in the Pohorje forests. Because of their participation in the National Liberation Front (OF) and the Resistance, many physicians, Sisters of Charity and other staff were arrested, tortured and even executed by the Nazis (Benčan, Strauch). After the bombing of Maribor's industry and railway

infrastructure, hospital activities were even more limited. The hospital was bombed as well, many of its buildings were damaged and some departments had to be moved. For this reason the maternity ward was moved to Ormož (60 km from Maribor) in 1944.

After the liberation in 1945, MGH was restored largely due to voluntary work. In a few months the work was nearly done and the professional management was able to begin solving the most urgent medical problems. First, pediatrics got its own department in 1946. Urgent problems were also trauma and blood donation. The Trauma Department got its rooms in 1949 and the Transfusiology Department was established in 1953. In 1948 the new so-called German building was finished to such an extent that the Department of Dermatology and Venereal Diseases was able to move there. In 1950 the ground floor of the same building was allocated to the Radiology Institute. At the same time also the Neuropsychiatric Ward, the Urology and Plastic Surgery Units each got their place. The Central Biochemical Laboratory was also established. In 1952 MGH got a new Department of Pulmonary Diseases, named after the physician Dr. Dušan Mravljak, a partisan killed on Pohorje in 1943. Finally in 1954, the Orthopedics and Thoracic Surgery Units were founded. In 1959 the first almanac of MGH was published, containing details on the development of our hospital from 1799 to 1955. In 1972 the Department of Psychiatry moved to Pohorski Dvor, and the surgical departments moved into the 16-floor building, which took 8 years to build and was completed at last in 1976. In 1979, an annex was constructed to this building, to house the Department of Anesthesiology and Reanimation and the operating theatres. Between 1982 and 1985 the construction of the new Department of Pediatrics took place. It was financed by local taxes imposed by a referendum. In 1983 a modern facility with nine operating theatres, a surgical emergency room and the Burns Unit was built. The third building, which was to house the Surgical Emergency Services, was opened in 1989.

On 22 May 1991, the new building for the Deptment of Obstetrics and Neonatology was opened, and in the following year the reconstruction of the Dept. of Gynecology in the “black building” was terminated. The new building and the reconstruction of our Gynecology Department were also financed by local taxes imposed by a referendum and paid for by the local population. The next

imposed tax enabled the opening of wings A and B of the Dept. of Internal Medicine. Recently the new buildings intended for the Department of Ophthalmology, the Department of Otorhinolaryngology and Cervicofacial Surgery and the Department of Psychiatry are under construction in the vicinity of the hospital. And finally, the reconstruction of the building for the new University of Maribor Medical Faculty was finished at the end of September of this year. The development and progress of MGH and its OBG part in the last decade is impressive.

After WW II, Slovenia got its second most important gynecological center at MGH. After 1950, screening for early detection of cancer using colposcopy and cytology was organized at the Department of OBG and radical abdominal as well as vaginal hysterectomies according to Wertheim and Schauta were performed. Contraceptive methods and family planning were systematically spread. Maribor gynecologists were the first in former Yugoslavia to develop amnioscopy, microanalysis of fetal blood and cardiotocography.

In the field of clinical obstetrics, MGH became the leading institution in entire ex-Yugoslavia.
Toward the end of 1960, endoscopic methods (laparoscopy and culdoscopy) were also used.

In the beginning of 1970, our physicians (Rostaher, Brumec, Japelj) were also the first in ex-Yugoslavia to publish an article on US diagnosis during pregnancy and gyneco-oncology.

Between 1970 and 1980 a number of new activities were introduced: breast oncology, gynecologic urology, operative endoscopy (laparoscopic or hysteroscopic) and all modern methods of infertility treatment. In 1989 our department was the third center in former Yugoslavia able to treat infertility with all methods of assisted reproductive technology (ART).

MGH currently employs 2426 medical and non-medical staff and with its 1473 beds provides medical care for people from the northern and northeastern part of Slovenia. Many physicians and other medical staff have been awarded academic titles. In 1991 MGH received the title of Teaching Hospital, cooperating closely with the Medical Faculty of the University of Ljubljana, the Secondary School

of Health Care in Maribor, the University College of Nursing Studies in Maribor, and with the new Medical Faculty of the University of Maribor founded in December of 2003. In 1995 two hospital departments received the title of clinical department (Clinical Department of Pediatrics, Clinical Department for Gynecology and Perinatology), two years later followed by the Clinical Department of Internal Medicine. The details regarding the medical history of Maribor and of MGH in particular are described in Almanac II (1955-1985), and especially in the publication Maribor General Hospital 1799 – 1999, at the opportunity of its 200-year anniversary.

GYNECOLOGY AND PERINATOLOGY SERVICE MARIBOR – FROM THE PRESENT TO THE FUTURE

Borut Gorišek

ABSTRACT

Maribor Teaching Hospital is the second largest medical center in Slovenia. The organogram of the institution shows the extremely broad field of expert activities going on here. Extremely variegated activities are also evident in the field of gynecology and perinatology. In accordance with modern trends this branch of medicine was also reorganized, going in the direction of reproductive medicine and perinatology, gynecologic oncology with breast oncology as well as endocrinology and gynecologic urology. Besides, physicians of the Gynecology and Perinatology Service have been active for decades in the field of teaching, at the Medical Faculty of Ljubljana as well as at the College of Nursing Studies in Maribor. Recently they are also teachers at the Medical Faculty in Maribor. Activities in the field of research are extremely important and physicians of the Gynecology and Perinatology Service are taking active part in national as well as international projects.

Key words: gynecology and perinatology, direction of future development, teaching activities, research activities

The present Maribor Teaching Hospital (MTH) consists of the following departments:

SURGICAL SERVICE
Department of Abdominal and General Surgery
Department of Vascular Surgery
Department of Traumatology
Department of Thoracic Surgery
Department of Urology
Department of Plastic and Reconstructive Surgery
Department of Neurosurgery
Department of Orthopedics
Department of Anestesiology, Intensive Care and Pain Management
Department of Cardiosurgery

JOINT SERVICES OF SURGICAL DEPARTMENTS
Surgical Emergency Services
Pediatric Surgery Division
Operating Theatres
Central Sterilization

INTERNAL MEDICINE SERVICE
Department of Rheumatology and Immunology
Department of Nephrology
Department of Hemodialysis
Department of Gastroenterology and Endoscopy
Department of Cardiology and Angiology
Department of Internal Intensive Care
Department of Hematology and Hematologic Oncology
Department of Endocrinology and Diabetology
Department of Nuclear Medicine

JOINT SERVICES OF INTERNAL MEDICINE
Emergency Internal Medicine
Outpatient Center

GYNECOLOGY AND PERINATOLOGY SERVICE
Department of General Gynecology and Gynecologic Urology
Department of Gynecologic Oncology and Breast Oncology
Department of Reproductive Medicine and Gynecologic Endocrinology
Department of Perinatology

OTHER INDEPENDENT MEDICAL DEPARTMENTS
Department of Otorhinolaryngology and Cervicofacial Surgery
Department of Ophthalmology
Department of Neurologic Diseases
Department of Infectious Diseases and Febrile Conditions
Department of Dermatology and Venereal Diseases
Department of Pediatrics
Department of Psychiatry
Department of Pulmonary Diseases

JOINT MEDICAL SERVICES
Department of Laboratory Diagnosis
Department of Radiology
Department of Transfusiology and Immunohematology
Department of Medical Rehabilitation
Department of Pathologic Morphology
Central Pharmacy
Medical Research Department

ADMINISTRATIVE AND TECHNICAL SERVICES
Personnel and Law Department
Purchasing Service
Financial Accounts Service
Economy and Analytics Service
Supply and Maintenance Service
Investment Bureau
Computer Center

DESCRIPTION OF ACTIVITIES

GYNECOLOGY AND PERINATOLOGY SERVICE

1) Coordinated creation of medical doctrine in the field of gynecology and perinatology.
2) Planning, guiding and coordination of working process between departments and activities.
3) Conducting and coordinating of financial and economic operations.
4) Conducting and coordinating of medical and nonmedical investments and purchase of medical and nonmedical equipment.
5) Staff policy making.
6) Cooperation with hospital management.
7) Cooperation with medical, educational and other institutions.
8) Coordinating and guiding of all training forms for all personnel.
9) Coordinating of teaching activities.
10) Planning and organization of professional meetings in Maribor and planning of participation in professional meetings elsewhere.
11) Organization, coordination and monitoring of medical research work.
12) Organization of work of nursing staff and assigning to departments and units.
13) Professional and organizational conducting of joint activities.
14) Public notice of duty, consultation and emergency activities.
15) Temporary or permanent transfer of physicians and other staff to other departments.
16) Weekly professional seminars, case presentations, Dept. Head's rounds.
17) Daily staff meetings.

Departments and Independent Activities

1) In accordance with professional directions of the joint professional board and the doctrine, they organize and carry out diagnosis, treatment and rehabilitation of patients in each specific field.
2) They take part in common tasks:
   a) Admission,
   b) Turns on duty,
   c) Counseling,

d) Intensive care and therapy,
e) Surgery.

3) They follow professional development and introduce novelties in their special field.
4) At meetings they report on their work and professional problems.
5) They work in accordance with professional and economic guidelines.
6) They give suggestions regarding staff policy, investments.
7) They give suggestions regarding all forms of staff education.
8) They carry out teaching and research activities.
9) They organize professional meetings.

Department of General Gynecology and Gynecologic Urology

1) Diagnosis and therapy of acute and chronic gynecologic inflammation.
2) Diagnosis and therapy of benign tumors.
3) Diagnosis and therapy of metrorrhagia and menstrual cycle disturbances.
4) Diagnosis and therapy of endometriosis.
5) Diagnosis and therapy of genital organ displacement.
6) Diagnosis and therapy of pathologic states in peri- and postmenopause.
7) Diagnosis and therapy of injuries to female reproductive organs.
8) Diagnosis and therapy of complications following artificial abortion.
9) Diagnosis, conservative and operative treatment of urogynecologic pathology.

Outpatient Clinics:

1) OPC for General Gynecology
   Diagnosis, treatment, counseling and prevention of gyn. diseases
2) OPC for Menopausal Women
   Diagnosis, treatment, counseling and prevention of diseases of pre-, peri- and postmenopause
3) OPC for US Diagnosis
   a) US diagnosis of gyn. diseases
   b) Diagnosis of endometrium
   c) Diagnosis of adnexal tumors
   d) Diagnosis of early pregnancy

4) Cabinet for Urogynecology
    a) Diagnosis and therapy of female urine incontinence
    b) Gynecologic examination
    c) Uroflowmetry
    d) Profilometry
    e) Cystometry
    f) Pad test
    g) Flow cystometry
    h) Electrostimulation of pelvic floor and bladder muscles and other methods of conservative treatment of urinary incontinence.

Department of Gynecologic Oncology and Breast Oncology

1) Detection and verification of primary site of malignoma.
2) Diagnosis of malignoma spread.
3) Diagnosis of general physical and psychic condition of oncologic patients.
4) Diagnosis of complications due to malignoma or malignoma treatment.
5) Treatment for malignoma of reproductive organs and mammae includes:
    a) Operative: radical, primary and secondary, palliative
    b) Cytostatic, hormonal and immunologic
    c) Generally medicamentous and analgesic
    d) Care, rehabilitation and physical therapy
    e) Psychotherapy.
6) Keeping of medical records.
7) Oncologic council
    a) Setting of indications and treatment plan
    b) Determining patients for treatment at OI and arranging transfer
    c) Attending to transfer of documentation.

Outpatient Clinics:

1) Center for Breast Diseases
    a) Detection and diagnosis of breast diseases
    b) Clinical breast examination
    c) Mammography and additional X-ray investigations
    d) US mammography
    e) Exfoliative and aspiration cytodiagnosis

f) Localization of unpalpable lesions
g) Mammographic imaging of biopsy specimens
h) Independent record-keeping.

2) OPC for Colposcopy
   Revision of colposcopic and cytologic findings, guided biopsy and independent record-keeping in:
   a) Women with smear showing severe cervical lesion
   b) Women with 3 - times abnormal smear
   c) Women after conization and assessed CIS or acc. to pathologist's recommendations
   d) Women before conization
3) OPC for US Diagnosis
   a) US diagnosis of gynecologic diseases
   b) Diagnosis of endometrial pathology
   c) Differential diagnosis of adnexal tumors
   d) Oncologic abdominal screening
4) OPC for Gynecologic Oncology
   a) Follows the condition of patients treated for gyn. malignoma, carries out regular follow-up investigations for early detection of recurrences and complications caused by the basic disease or therapy.
   b) Treats complications and concurrent diseases in oncology patients.
   c) Keeps medical records independently.
5) OPC for Breast Oncology
   Same as in patients with breast cancer.
6) OPC for Psychooncology
7) OPC for Chemotherapy

Department of Reproductive Medicine and Gynecologic Endocrinology

1) Diagnosis and treatment of female and male infertility.
2) Operative treatment of female infertility.
3) Testicular biopsy in infertile men.
4) Laparoscopy, hysteroscopy, HSG, etc.
5) Diagnosis and therapy of female endocrinologic disturbances.
6) Diagnosis and therapy of developmental anomalies.
7) Diagnosis and treatment of spontaneous and threatening abortion.

Outpatient Clinics:

1) OPC for Female Infertility
   a) Assessment of causes of female infertility and their treatment
   b) Counseling in reproductive treatment
2) Andrologic OPC
   a) Assessment of causes of female infertility and their treatment
   b) Counseling in reproductive treatment
3) OPC for Gynecologic Endocrinology
   a) Diagnosis and treatment of endocrinologic genital disturbances
4) OPC for Birth Control
   a) Introduces new methods of contraception and follows their effectiveness and complications
   b) Follows the extent and complications of hormone and intrauterine contraception
5) OPC for High-Risk Early Pregnancy
   a) Monitors high-risk pregnancies particularly after assisted reproduction and recurrent abortion
6) OPC for Juvenile and Adolescent Gynecology
   a) Diagnosis and treatment of gynecologic disturbances in adolescents
   b) Counseling in prepuberty and puberty
7) OPC for US Diagnosis
   a) Control of pregnancy the first 12 weeks after assisted reproduction
   b) Control of all high-risk pregnancies and diagnosis of pathologic pregnancy
8) OPC for Assisted Reproduction
   a) Monitoring of patients receiving hormone therapy for stimulation of ovulation, particularly in application of analogues and gonadotropins
   b) US folliculometry and cycle registration

Facilities:

1) Laboratory procedures for all assisted reproduction techniques
   a) Insemination, IVF, GIFT, ICSI, TESE etc.
   b) Sperm bank
2) Andragogic Laboratory

a) Performs all ejaculate investigations according to WHO standards
b) Performs all superstandard gamete investigations

Department of Perinatology

1) Diagnosis of risk in pregnancy.
2) Diagnosis and therapy of pathologic conditions in pregnancy and assessment of optimum term for termination of pregnancy.
3) General and obstetric clinical examinations.
4) Laboratory analyses - hematologic, biochemical, hormone, genetic.
5) US investigation.
6) US flowmetry.
7) Amnioscopy.
8) Cardiotocography.
9) Care for healthy puerperae and counseling in establishing a mother-child relationship.
10) Diagnosis and therapy of diseases in puerperae, care and counseling in establishing a mother-child relationship.

Facilities:

1) Maternity Ward
   Monitoring of normal and pathologic deliveries
   a) Clinical general and obstetric examination
   b) Cardiotocography
   c) Analysis of fetal blood pH
   d) Amniotomy
   e) Delivery induction and stimulation
   f) Manual help, vacuum extraction, etc.
   g) Episiotomy and suturing of episiotomies and ruptures
   h) Revision of soft birth canal, manual exploration of uterus, manual removal of placenta, abrasion of the uterus
   i) Delivery pain management
   j) Primary care of neonates

2) Intensive Care
   a) Intensive care after surgery or pathologic delivery
   b) Intensive monitoring of pathologic pregnancies

Outpatient Clinics:

1) OPC for High-Risk Pregnancy
   a) Clinical general and obstetric examination
   b) Hormone and biochemical analyses
   c) US assessment of gestation age, monitoring of growth, assessment of vital parameters
2) OPC for Cardiotocography, Initial Examinations and Consultations
   a) Clinical and cardiotocographic examination for determination of optimum term for delivery and detection of fetus at risk
   b) All admissions to obstetric dept.
   c) Consultatory examinations of pregnant women from all MTH departments
3) OPC for US Diagnosis
   Prophylactic and diagnostic investigations
   a) Determination of pregnancy
   b) Investigation of anatomy and detection of anomalies
   c) Determination of gestation age
4) OPC for Diagnosis of Anomalies
   a) US investigation
   b) Hormone diagnosis of chromosome anomalies
   c) Early AC and CVS
5) OPC for Genetic Counseling
   Discussions, counseling and indication of investigations
6) School for Expectant Parents

Division of Neonatology

1) Unit for Healthy Neonates
   a) Care and monitoring of healthy neonates, counseling and help in establishing a mother-child relationship
   b) Daytime rooming-in and night station
2) ICU I. degree for neonates
   Diagnosis, I. degree intensive care and therapy for neonates

Duty staff:

Physicians of Division of Neonatology

Outpatient Clinics:

1) OPC for Neonates at Risk
2) OPC for US Investigation of Neonates
   a) US of head - diagnosis of lesions

b) US of hips - detection of dysplasias
c) Abdominal US - detection of anomalies of gastro-urinary tract

3) OPC for Neonates from discharge to one month
   a) Monitoring of the infant's development in the neonatal period

JOINT ACTIVITIES

1) ADMISSION OF PATIENTS
   a) OPC for admission of patients to both depts.; over 6000 patients/year

2) ICU
   a) Intensive monitoring and care after surgery
   b) Intensive therapy I. and II. degree

3) OR I. and II.
   a) 2 ORs for major aseptic operations (abdominal and vaginal)
   b) 1 OR for laparoscopic and hysteroscopic diagnosis and surgery
   c) 1 OR for septic operations
   d) 1 OR for embryotransfer
   e) 1 OR with 2 op. tables for minor surgical procedures
   f) 1 OR for cesarean sections
   g) 1 OR for minor obstetric operations

4) Day Clinic
   10 beds for recovery after short anesthesia for:
   a) Artificial termination of pregnancy
   b) Diagnostic and therapeutic abrasion
   c) Marsupialization
   d) Excisions, incisions, ablations, etc.

5) Administration
   Administration for all OPCs and depts.

6) Chief Office for appointments and outpatient activities (I and II)
   a) Appointments in person or by phone for OPC examinations
   b) Information about OPC work

7) Counseling and Duty Activities

a) Specialists are engaged in counseling after public official notice.
b) After public official notice, physicians and SRNs perform their work when they are on duty, out of regular working hours.

8) Specialist and Subspecialist OPCs

1. OPC for General Gynecology
2. OPC for Peri- and Postmenopausal Women
3. OPC for US Diagnosis
4. Cabinet for Urogynecology
5. Center for Breast Diseases
6. OPC for Colposcopy
7. OPC for Gynecologic Oncology
8. OPC for Breast Oncology
9. OPC for Psychooncology
10. OPC for Chemotherapy
11. OPC for Female Infertility
12. Andrologic OPC
13. OPC for Assisted Reproduction
14. OPC for Gynecologic Endocrinology
15. OPC for Birth Control
16. OPC for High-Risk Early Pregnancy
17. OPC for Juvenile and Adolescent Gynecology
18. OPC for High-Risk Pregnancy
19. OPC for Cardiotocographic Monitoring of Pregnancy
20. OPC for US Diagnosis
21. OPC for Initial Examinations and Consultations
22. OPC for Genetic Counseling
23. School for Expectant Parents
24. OPC for High-Risk Neonates
25. OPC for US Examination of Neonates
26. OPC for Neonates from discharge to one month

9) Psychology

a) Psychooncology
b) Pre- and postoperative psychotherapy
c) Psychotherapy of infertile couples
d) Psychotherapy and psychologic support of pregnant women and puerperae
e) Psychotherapy in perimenopause

10) Physical Therapy

a) Physical therapy of oncologic female patients
b) Physical therapy after gynecologic operations
c) Physical therapy in pregnancy and after delivery
d) Physical therapy of urogynecologic patients
e) School for parents

11) Teaching Activities

a) Preparation of lectures for medical school students
b) Lectures at secondary medical school and others
c) Practical work for students of Ljubljana Medical School and others
d) Practical work for students of higher and secondary medical schools
e) Schooling, seminars, practical training of assistant physicians, residents and other forms of postgraduate training
f) Popular-scientific lectures
g) Writing of manuals, lecture notes and popular-scientific papers

12) Medical Research Activities

a) Preparation of research projects
b) Cooperation with Medical Research Department at MTH and other research units outside the hospital
c) Coordination and execution of research projects

Independent Activities

1) Laboratory of Cytodiagnosis

a) Receives and keeps records of cytologic specimens from gynecologic and obstetrics OPCs, departments and health centers from the Maribor region
b) Fixes and stains the specimens
c) Analyzes the specimens, reports on the findings and advises
d) Follows patients with pathologic findings
e) Keeps archives of smears and keeps records
f) Follows doctrinal development and controls the quality of work in OPCs
g) Educates gynecologists in this special field

2) Laboratory of Medical Genetics

a) OPC for genetic counseling
b) OPC for prenatal diagnosis
   Anamnesis, heredogram, clinical examinations, X-ray, US, cytogenetics, fetoscopy, amniocentesis, placentesis, chordocentesis
c) Laboratory of Cytogenetics

The Departments of Gynecology and Perinatology cooperate professionally with all other MTH departments, with the Ljubljana Institute of Oncology and Clinic of Gynecology.
The Department of Anesthesiology with the ICU for surgical departments, the Department of Transfusiology, the Department of Radiology and the Hematological, Biochemical and Hormone Laboratories as well as the Department of Pathologic Morphology are at about a 100 m distance from the Deptments of Gynecology and Perinatology.

The layout of the Department of Perinatology is quite modern. It is housed in a building built 10 years ago. The same is true of the Departments of Gynecology, which moved into a completely reconstructed building 8 years ago.

The rooms at the Department of Perinatology are equipped with electronic monitoring, a pH-metry device, cardiotocography, etc. The OR for cesarean sections is located within the block of delivery rooms.

Every woman is admitted to the Maternity Ward by a specialist. If labor has already begun, the woman is placed in the delivery room where she is under the constant control of a specialist, a resident and a midwife - through 24 hours. The delivery rooms have no video-film system.

FACILITIES

The Department of Gynecologic Oncology and Breast Oncology are engaged in differential diagnosis, operative treatment, systemic treatment of all gynecologic and breast carcinomas. All radiotherapy

in our patients is carried out by the Ljubljana Institute of Oncology. After termination of treatment, such patients have special follow-up OPCs at their disposal. Within this Department is also the Laboratory of Cytology, a special OPC for Colposcopy, Center for Breast Diseases and the oncologic OPC for patients with gynecologic or breast cancer.
For the past 10 years we have been developing endoscopic surgery techniques such as laparoscopy and hysteroscopy since we have over 30 years of experience in the field of laparoscopic diagnosis.

In 1969, the Maribor Department of Gynecology was the first in former Yugoslavia to engage in US diagnosis and at that time represented the center for such diagnosis in the country.

Since 1991 we have a Cabinet for Urodynamics with modern operative and conservative therapy for incontinent patients (Burch, TVT, electrostimulation, medicament therapy and other).

At the Departmet of Reproductive Medicine we carry out assisted reproduction (about 600 cycles per year) with the newest ICSI techniques etc.

The Department of Perinatology also comprises the Division of Neonatology with 5 pediatricians - neonatologists. Intensive care is carried out at the Maternity Ward, intensive therapy at the ICU in the adjoining building of the Pediatric Dept.

The anesthesiology service is organized centrally for the entire hospital. Three physicians - anesthesiologists daily are at the disposal of our departments. Due to the lack of anesthesiologists, deliveries in epidural anesthesia are only carried out sporadically.

The Department of Pathologic Morphology is at the disposal of our entire hospital. However, our pathomorphologists are specialists in specific fields, gynecologic pathomorphology included. It is mandatory for clinical physicians to be present at post-mortem examinations. A month of training at the pathomorphology department is in the study plan of residents.

We have six ORs completely equipped for surgery using classical techniques as well as endoscopic techniques with video-system.

Residents carry out the entire program under the obligatory supervision of their mentors.
With regard to the large population and additional concentration of pathology from smaller neighboring hospitals, residents have ample possibility to become acquainted with all the necessary fields.

The residents learn special techniques of diagnosis and therapy such as US diagnosis, endoscopic surgery and others during special courses organized at our department and at the Ljubljana Gynecology Clinic, but also within the regular program for clinical work at our department.

The specialist OPCs include four OPCs for general gynecology working according to the primary health care method of work. Our specialist OPC activities are also evident from the organogram. We examine 26.335 patients yearly. However, OPC activities are the domain of the Health Center and the private practice of gynecologists and obstetricians.

The specialization training also includes obligatory turns on duty during which the trainees performs emergency surgery under the mentor's supervision.

Family planning goes on in all OPCs. There is also an OPC for birth control. In the range of our service, a commission for the approval of sterilization and abortion is also active.

Physicians from the Gynecology and Perinatology Service carry out numerous research projects under the auspices of the Slovene Ministry of Science and Technology and the Municipal Research Council of Maribor.

TEACHING ACTIVITIES

Medical doctors working at the Gynecology and Perinatology Service of General Hospital Maribor in the past decades were always also lecturers at the Secondary School for Nurses in Maribor. Ten years ago the College of Nursing Studies was founded within the University of Maribor and since then the subject of gynecology and perinatology is included in its study plan. Lectures and practical work is lead by

habilitated teachers employed at our Gynecology and Perinatology Service.
Since 1980 habilitated teachers working at our departments have been lecturing regularly and carrying out part of the program for students of general medicine at the Ljubljana University Medical Faculty.
In 2004 the University of Maribor Medical Faculty was founded, with a complete program for preclinical and clinical studies for students of general medicine. The staff of habilitated teachers includes two full professors and two associate professors, four assistant professors and ten assistants, all of which will carry out the whole program (lectures, practice) covering gynecology and perinatology in the 5th year of medical studies.

Research activities

At General Hospital Maribor, research is organized at every department. Besides, expert and technical support is offered by our Medical Research Department. Physicians and others employed at our Departments of Gynecology and Perinatology have in the past decade performed more than 60% of the whole research going on at our institution. With the founding of the Maribor Medical Faculty, the College of Nursing Studies and due to cooperation with the Medical Faculty in Ljubljana, scientific and research work at our Departments is even more intense. We are involved in several international research projects.

CONCLUSIONS

A review of the professional activities going on at present at the Maribor Teaching Hospital Gynecology and Perinatology Service shows the direction of further development of this special field of medicine. It follows modern trends in the development of medical science in Western Europe. In recent years there is evidence of more intense work in the field of teaching while scientific research work has already been extremely active for several decades.

ASSISTED REPRODUCTION TECHNIQUES IN SLOVENIA
Recent research projects of the Maribor ART Center

Veljko Vlaisavljević

The current year brought the 20th anniversary of the first clinically successful *in vitro* fertilization (IVF) procedure carried out in Slovenia, at the Ljubljana University Hospital Department of Gynecology. At the Maribor Teaching Hospital (MTH) Gynecology and Perinatology Depts., the beginnings of "assisted reproduction techniques", later named "fertilization by means of biomedicine" (FMB), reach back to the year 1983. The establishment of this field of activity - we simply called it "the IVF program" while our patients called it "the test tube" - represented the basis for rich professional and research activities in the management of infertile couples in Maribor. The Department of Reproductive Medicine and Gynecologic Endocrinology at MTH developed rapidly into a modern and top-level medical institution. Numerous FMB procedures, which had been transferred to Slovenia and whose results have been published at home as well as abroad, serve to confirm this statement. In past years even prominent foreign journals have reported on the achievements of Slovene reproductive medicine: *Human Reproduction*, *Fertility Sterility*, *Human Reproduction Update*, *Zygote*, *Journal Of Assisted Reproduction and Genetics*, *Journal of Reproductive Medicine*, *Ultrasound in Obstetrics and Gynecology*, *International Journal of Obstetrics and Gynecology*, *Reproductive BioMedicine Online* and others.

In its efforts to introduce new methods of treatment, Slovenian reproductive medicine was quick to follow the world trends. The level of reproductive medicine in former Yugoslavia is best illustrated by the fact that the first baby born post IVF in that country meant a placing among 8 centers in the world which had succeeded in crowning their endeavors with clinical success. Present endeavors for a decrease in the number of multiple pregnancies following FMB and for quality IVF/ICSI procedures also place Slovenia

among the developed countries in Europe. The concern of the state for the treatment of infertility is also evident from the fact that four FMB procedures in each patient are carried out at the expense of health insurance, which is an exception rather than a rule in European countries.
The historical development of the introduction of modern FMB methods in Slovenia shows a minimum delay with respect to world events (sometimes only a few months). The introduction of novel methods went on almost simultaneously at both university hospital departments in Ljubljana and Maribor, or perhaps with a few months' interval. At present both departments carry out all treatment techniques known by modern medicine, preimplantation genetic diagnosis (PGD) included.
Work at all three institutions holding the license for FMB is proceeding in conditions of cooperation and professional consultation, thus leading to better results than if legal restrictions had been considered (e.g. the law allows the transfer of 3 embryos while inter-center agreement allows only 2) (Table 1).

A comparison of the results of treatment using procedures of FMB in Slovenia with the latest data published by the European Register of FMB for 2001 shows the high standard of services offered by our institutions. Indicators of the quality of services performed (choice of method of treatment, choice of medications and protocols for ovulation stimulation, percentage of oocytes fertilized, rate of embryotransfer, delivery rate per started cycle, relationship between transfer of one, two or three embryos and the percentage of successful follow-up of babies born) place the results obtained at our centers into the top third of all results obtained, at any rate above those considered to be the European average.

RESEARCH

Since the founding of our IVF center, apart from clinical work we have been engaged in research work as well. With the results of our research we wish to contribute our part to the basic knowledge in the field of reproductive medicine, at the same time directly introducing the acquired knowledge to improve routine clinical work. Particularly from the viewpoint of applicability the research projects are extremely

significant for our patients also, since the results of the studies contribute essentially to the quality of health care.

We are presenting our main research projects of the past few years. Some have already come to a close and the results reported at professional meetings at home or abroad and published in the professional literature at home or abroad. Some of the projects are financed by the Ministry of Education, Science and Sport of the RS, others form part of international projects. All projects were approved by the Medical Ethics Committee of the RS.

- Characteristics of the dominant follicle in unstimulated cycles
- Characteristics of antral follicles and maturation capacity of oocytes under *in vitro* conditions
- Computer program for identification of antral follicles in 3D image of ovary during controlled hyperstimulation
- Biochemical markers for identification of blastocyst implantation capacity
- Preimplantation genetic diagnosis
- The significance of transvaginal hydrolaparoscopy in infertility management
- Cryopreservation of blastocysts
- A comparison of media for 5-day cultivation of embryos
- Clinical success of ovulation stimulation using gonadotropins of urinary and recombinant origin (MERIT Study)
- Clinical success of ovulation stimulation protocols with recombinant gonadotropins and antagonists of gonadoliberin (Stars in ART Study)

Accessibility No. FMB cycles per 1 million inhabitants	Percentage of babies born, conceived by FMB (%)	Percentage of pregnancies per embryotransfer post IVF (%)	Percentage of pregnancies per transfer post ICSI (%)	**Quality** Percentage of cycles with transfer of more than 2 embryos post IVF and ICSI (%)
Denmark 1923	Denmark 3.9	Iceland 36.9	Latvia 57.7	Sweden 2
Finland 1486	**Slovenia** 3.3	Latvia 36.4	Iceland 36.5	Finland 3
Iceland 1410	Sweden 2.8	**Slovenia** 36.2	Netherlands 36.2	Denmark 7
Sweden 1133	Iceland 2.7	Norway 34.4	Greece 36.2	**Slovenia** 16
Slovenia 1122	Finland 2.4	Russia 34.1	Spain 33.7	Iceland 20
Babies born in Slovenia (2001): **579** Maribor 254 (44 %) Ljubljana 220 (38 %) Postojna 105 (18 %)		**Maribor 54.9**	**Maribor 44.9**	**Maribor 3**

Table 1. The first five European countries classified acc. to success regarding the results of FMB. Source: European Register of FMB for 2001 (ESHRE report 2004)

TUBAL INFERTILITY

Milan Reljič

Infertility is defined as one year of unprotected coitus without conception. It affects approximately 10-15% of couples in the reproductive age group and among them tubal infertility accounts for approximately 30 to 40% of cases.

PHYSIOLOGY AND PHYSIOPATHOLOGY

The fallopian tubes are fundamental for human reproduction. They are part of the female reproductive system, along with the vulva, the vagina, the uterus and the ovaries. The fallopian tubes are two tubal structures that can measure between 7 and 12 cm in length. Basically they are formed by smooth muscle, covered by a peritoneal layer and in the interior they are lined by delicate epithelium. Their function is to capture the egg when it is released from the ovary and to transfer the egg in their interior, where eventually it will meet with the sperm ascending from the vagina, achieving fertilization. The first stage of development of the embryo occurs in the fallopian tubes during the four days that it takes for its transfer to the uterine cavity, where it is finally implanted. Damage of tubal structure and function can interfere with any step of this process and may lead to infertility.

Due to their structure, the fallopian tubes are easily affected by certain diseases. The tubal lumen is narrow and the epithelium is very delicate, which makes it more susceptible to damage than other structures of the female reproductive system. They can suffer various changes related to pathological agents, such as endosalpingeal damage, wall thickening, lumen blockade (distal and proximal), and peritoneal peritubal adhesions with disturbance of the tubo-ovarian spatial relationships.

Causes of tubal pathology

In nine of every ten cases, the cause of tubal infertility is a pelvic inflammatory disease (PID) secondary to a sexually transmitted disease (STD). The etiologic relationship between STD, lower genital tract infection, PID and tubal infertility involves a multifactor multistep process. Acute polymicrobial PID beginning with a cervical infection with sexually transmitted pathogens continues with an alteration of the vaginocervical microenvironment and an overgrowth of vaginal facultative and anaerobic flora resulting in lower genital tract infection, to progress with the ascent of pathogens into the endometrium, the fallopian tubes and the peritoneal cavity. Frequently, the infection is polymicrobial, but the primary compromise is usually produced by sexually transmitted bacteria. Of the twenty or more microoganisms that are usually transmitted by sexual contact, only two or three bacteria are capable of producing PID. They are Neisseria gonorrhoea, Chlamydia trachomatis and possibly some species of the Mycoplasma. Infection by Chlamydia trachomatis is the most significant cause of PID, not only because of prevalence but also due to its characteristics. The Chlamydia infection is most frequently (70%) asymptomatic and prolonged, making it more difficult to diagnose. In contrast, gonococcus infection is usually symptomatic and acute, associated with abnormal vaginal discharge, fever and pelvic pain. Certain kinds of Mycoplasma have been cultivated from the endometrium and from the fallopian tubes in cases of PID. Although their pathogenic power is not questionable, their real role as primary invaders in PID is not completely clear.

Infection can also propagate from the lower genital genital tract to the tubes after intrauterine procedures done under inadequate conditions, after spontaneous abortion and prolonged or traumatic birth. Other infection located in the pelvis can affect the fallopian tubes due to the proximity, as is the case with appendicitis.

Tubal ectopic pregnancy is a serious and frequent problem and can damage the fallopian tubes, but more than a cause, it is the consequence of previously established tubal pathology.

Endometriosis is the principal non-infectious cause of definitive damage to the fallopian tubes due to the peritoneal inflammatory

response. Other causes of tubal pathology such as genital tuberculosis, uterine fibromas and tubal agenesia are very rare.

DIAGNOSIS

Today four diagnostic techniques are used to explore the tubal factor in the sterile patient:

- Hysterosalpingography
- Hysterosalgingosonography
- Endoscopic techniques (laparoscopy, transvaginal hydrolaparoscopy)
- Test for Chlamydia

Hysterosalpingography consists of an injection of an iodine contrast (liquid opaque to X-rays) through the neck of the uterus, filling the uterine cavity and the tubes, in an indirect manner allowing the radiological study of the anatomical characteristics of the lumen of these organs. This technique can reveal several tubal pathologies: obstruction, dilatation, stenosis, polyps and old tuberculosis infections. It is a method of screening that can be applied on an outpatient basis, is easy and inexpensive. But generally it does not permit an etiologic diagnosis, and it does not reveal either the serous plane (external) of the tube or the tubal environment. Occasionally, tubal spasms are produced that are indistinguishable from true obstruction. But this is only one reason why sensitivity and specificity are not very high (0.65 and 0.83). Complications are rare, but infection (especially in pathological tubes), uterine perforation, anaphylactic shock and interruption of unsuspected pregnancy have been described. Nevertheless, the radiation to which the patient is exposed is minimal and is not considered harmful.

Hysterosonosalpingograpy is ultrasonic exploration of the uterus and of the tubes, where a fluid is injected through the uterine cervix in order to create an acoustic window of differing echogenicity, allowing better observation of the internal wall of these structures. In normal tubes the flow of the injected liquid can be seen, especially in the proximal part. On finalizing the exploration, it is observed how the liquid is found in the bottom of the pelvis. If Doppler velocimetry is available, a continuous signal during contrast

injection confirms tubal permeability. Unilateral or bilateral tubal obstructions can be diagnosed. Anyway, the information given is very reduced. Only tubal permeability can be studied, and even that cannot be precisely located. Tubal spasm that is indistinguishable from an obstruction can be set off. No information regarding the characteristics of the three tubal planes is gained. Complications are rare. Minor adverse effects such as pain, generally light and tolerable, vasovagal reactions, nausea, vomiting, hyperventilation and sweating have been described.

Tests for Chlamydia are blood tests with the objective of determining the existence of an infection by Chlamydia, which has been stated as the infectious agent most frequently affecting the tubes. They are serological tests that are based on the detection of antichlamydia antibodies, which persist long after the infection occurs. In fact, one positive test alone cannot determine if the infection is current or an old one. Sensitivity and specificity varies between 0.20 and 1.00 according to the test considered, of which there are many. Obviously, it is not an aggressive test and it is inexpensive, but it does not allow for the diagnosis of other possible infectious agents, and it does not offer information about the anatomical state of the tubes and therefore should complement other existing methods.

Laparoscopy is the technique that allows the direct observation of the peritoneal cavity contents, and therefore the exterior of the tubes and their surroundings through a rigid endoscope introduced through the abdominal wall. It is a method that can best establish the prognosis of a tubal pathology, decide on the suitable therapy, and often allows for the surgical maneuvers that correct certain tubal anomalies and anomalies of other types in the same surgical procedures. The tubal abnormalities that can be diagnosed correspond to obstruction, stenosis, inflammation, hydrosalpinx, dilatation, diverticula, peritubal adhesion, agglutination of fimbriae. The salpingoscope may be introduced by laparoscopy and direct visualization of the internal wall of the ampulla is possible (*salpingoscopy*). The pathological images that can be obtained by salpingoscopy correspond to adhesion, polyps, stenosis, dilatation, obstruction, and atrophy of the mucosa. Laparoscopy requires general anesthesia and hospital admission. Complications are rare but serious, including the anesthetic, perforations, hemorrhages,

burns, infections, and complications relating to the insufflations of gas. *Transvaginal hydrolaparoscopy* (THL), which is performed under local anesthesia, is a new culdoscopic technique for exploring tuboperitoneal infertility. In this procedure a dilating trocar is inserted through the posterior vaginal wall for endoscopic pelvic examination. Normal saline is used to float the bowel out of the pelvis so that one can evaluate the distal fallopian tubes, ovarian surfaces, pelvic sidewalls, and cul-de sac. The most common complication of THL is extraperitoneal bowel lesion, which tends to be a minor lesion, managed expectantly. THL is an accurate, minimally invasive and well-tolerated diagnostic method, which could replace HSG and/or laparoscopy in some cases, but its role in infertility evaluation is not yet clearly defined.

THERAPY

There are two options for a couple with tubal infertility to achieve a pregnancy: reconstructive tubal surgery and in vitro fertilization (IVF). Selection of the most appropriate treatment is based on the outcome of the treatment in the individual couple, the acceptability of the treatment modalities and in a cost conscious society, the cost-effectiveness. There are cases of infertility in which both techniques may be applied and we must recommend one or the other according to the characteristics of each patient, individualizing the strategy to be used in each case. However, IVF and tubal surgery should not be considered as competitive and mutually exclusive, but as complementary procedures, which can be applied with appropriate chronological consequences. Anyway, there are clear indications for advising each one of the techniques.

Tubal surgery

Laparoscopic tubal surgery is the treatment of choice in the young patient with limited tubal pathology. But the main counter-indications for tubal repair by laparoscopy are severe pelvic adhesions with a »frozen pelvis«, past history of extensive tubal resection for sterilization, thick wall hydrosalpinx, extensive intra-ampullar adhesions and complete destruction of the mucosa, bifocal

tube disease, ongoing genital tuberculosis or sequelae, the existence of associated incurable factors for infertility and older patient age.

The first phase of the operation must always be devoted to adhesiolysis. The *adhesiolysis* is essential to restore a normal anatomical relationship and perfect mobility of the tube relative to the ovary. Once this adhesiolysis has been carried out the tubal lesions can be assessed more accurately. The morphology of the tubes is evaluated and their patency checked using the methylene blue test. Further surgery depends on the tubal pathology.

The principle of *fimbrioplasty* is to restore the original anatomy of the infundibulum by treating the phimosis. The technique of *salpingostomy* consists of creating a new ostium in cases when the distal part of the tube is totally occluded (hydrosalpinx). The operation comprises two phases, incision and eversion.

Tubal block at the cornua can be a result of infection, sterilization or endometriosis. This obstruction can be overcome with *cornual anastomosis,* which includes the identification of the intramural portion of the tube by careful shaving of the cornua and then joining the healthy isthmus or ampulla directly to the intact intramural portion of the tubes. In some selected cases of cornual block, *tubal cannulation* (or catheterization) can also be employed. The nature of the blocks that can be treated by tubal cannulation is either the accumulation of material or debris - often of endometrial origin - making a kind of plug that can be pushed away by the cannula and the washing liquid, or mucosal synechia, the folds having been glued on the occasion of an inflammatory process (often post partum or post abortum). Results can be very good when the indication is correct.

The fertility results for laparoscopic tubal surgery depend on the severity of the tubal damage and pelvic adhesions. There is a particularly good correlation between the quality of the mucosa and the intra-uterine pregnancy rate, varying between 0 – 60%. Most pregnancies occur within one year of the operation. The major advantage of tubal surgery is that it can restore fertility. Consequently, it allows conception without the need for further treatment. Tubal surgery avoids many of the moral, ethical and religious dilemmas associated with IVF. The disadvantages of tubal

surgery are mainly associated with the performance of a major surgical procedure, the requirement of anesthesia and hospitalization. Tubal surgery is also associated with the risk of ectopic pregnancy.

In vitro fertilization

Tubal pathology has classically been considered as the major indication for performing IVF. IVF is the therapeutic option of choice in cases of severely damaged tubes where the prognosis of tubal surgery is not good, in women older than 35 years, if there are other associated infertility factors and if pregnancy has not been achieved one year after any type of tubal surgery.

The procedures involved in IVF treatment can conveniently be considered under six steps: stimulation of ovulation, monitoring of ovarian stimulation, oocyte retrieval, in vitro fertilization, embryo assessment and transfer, and lutheal support.

To discover the real efficiency of IVF we can consult different registers which coincide reasonably well in stating that the live-birth rate is influenced by the cause of infertility and above all by the age of the patient. Most statistics publish conception rates after 3 IVF cycles as being close to 50 %. There are severe tubal pathology situations which compromise ovarian vascularization where the IVF yield is lower. Likewise, in cases of big hydrosalpinges it seems that embryo implantation is altered with bilateral salpingectomy being recommended in these cases when they have repeated implantation failures. That is to say that in evaluating the efficiency we must bear in mind that it is appropriate to recommend IVF when tubal surgery does not offer a possibility of pregnancy greater than 30 – 40% after one year of follow-up, or a monthly conception rate - if this can be calculated - of less than 2%. Certainly, there are differences between the two techniques since IVF is a palliative technique, which does not cure the problem, while tubal surgery should be considered a curative treatment. Likewise there are other aspects to be taken into account such as the reproducibility of IVF, which is greater than that of tubal surgery, as well as the possibility that IVF offers the possibility of treating infertility of multi-factor origin. One of the major advantages of IVF is that the procedure can be performed in an office setting and

the pain can be managed with analgesics. In addition, the outcome of the treatment is usually known to the patient within two weeks. The medical risk associated with IVF is related to the use of ovarian stimulation. This can lead to the ovarian hyperstimulation syndrome, which is occasionally severe enough to require hospitalization. Multiple pregnancies, preterm labor and neonatal complications are also more common. Although high order multiple births can be reduced by limiting the number of embryos transferred, the possibility of twins is still higher than with tubal surgery. The potential risk of ovarian cancer resulting from the use of fertility drugs has caused concern, but the evidence for a casual association is still unproven. Complications of the procedure such as infection and bleeding can occur, but they are rather infrequent and usually easily managed. The overall risk of developing tubal pregnancy after IVF is quite low, but is increased in patients with distal tubal disease.

PREVENTION

The prevention of tubal disease is the prevention of STD and their sequelae. Prevention can either consist of screening high-risk groups for the presence of disease (post-hoc prevention of tubal infertility by early detection and treatment of PID), or at primary prevention of PID (and subsequent tubal infertility) by educational and prevention strategies aimed at the adolescent.

Teenagers are at higher risk for STD than any other age group, for a variety of reasons: the presence of cervical ectopy, their relative lack of protecting neutralizing antibodies, the occurrence of anovulatory cycles with easily permeable cervical mucus, the lack of contraceptive usage, their risk-taking behavior, their poor motivation for diagnosis and treatment, their poor compliance for follow-up. Traditional prevention efforts have frequently been proven ineffective in a teenage population. Peer-led education, training, and skills building, backed up by service availability, emerges as the most appealing. Adolescents will adopt health behavior more easily from their peers, who are more likely to convince them that they are susceptible to the problem, and that the problem has severe consequences for their future fertility.

The secondary prevention is the screening of individuals at risk and treating them before PID develops and irreparable tubal damage will

have occurred. Among the risk factors for contracting STD are: young at first sexual intercourse, higher life-time number of sexual partners, fewer years of education, lower socio-economic class, lack of contraception, present intrauterine contraceptive device use and prior history of PID.

Finally, increasing the awareness of doctors and other health care professionals of the (lack of) symptoms of atypical PID and of the need for early treatment will further decrease the risk of tubal infertility developing.

Suggested reading:

1. Meden-Vrtovec H et al, eds. Neplodnost. Ljubljana: Cankarjeva založba, 1989.
2. Speroff L, Glass RH, Kase GN, editors. Clinical gynaecologic endocrinology and infertility. 5th ed. Baltimore, Philadelphia, Hong Kong, London, Munich, Sydney, Tokyo: Williams & Wilkins, 1994.
3. Edvards RG, Brody SA, eds. Principles and practice of assisted human reproduction. Philadelphia, London, Toronto, Montreal, Sydney, Tokyo: W.B. Saunders Company, 2000.
4. Aristizabal J, Barri PN, Brosens IA et al. Tubal infertility. IFFS international consensus, 2001.

OVERVIEW OF THE LABORATORY PROCEDURES RELATED TO HUMAN GAMETES AND EMBRYOS

Borut Kovačič

INTRODUCTION

The complete treatment of infertile patients requires well-equipped biological laboratories for the handling of human gametes and embryos, enabling us to perform the various diagnostic procedures and sophisticated biotechnological techniques. Despite this, there are different sized laboratories for assisted reproductive techniques (ART), from small units having only a microscope for quick evaluation of some semen parameters to bigger centers where laboratories are specialized for semen assessment and preparation of specimen for insemination (andrology laboratory), for in vitro fertilization (IVF) and microfertilization (ICSI - intracytoplasmic sperm injection) techniques (IVF and ICSI laboratory), for cryopreservation of gametes and supernumerary embryos (cryo laboratory) and for preimplantation genetic diagnosis (PGD laboratory). In most centers for infertility treatment all procedures are performed in one laboratory, usually named IVF laboratory.

Successful assisted reproduction involves the careful co-ordination of both a medical and a scientific approach to each couple undertaking a treatment cycle. The responsibility of the IVF laboratory is to ensure a stable, non-toxic, pathogen-free environment with optimum parameters for oocyte fertilization and embryo development. Because multiple variables are involved, each step must be carefully controlled.

The hightech procedures require a well-trained staff. Since most of the techniques are in the phase of development, and because the success of treatment with ART is significantly dependent on the laboratory, scientists, biologists as well as specialized technicians are involved in the clinical program.

SEMEN ASSESSMENT

From the results of semen analysis we can never predict whether a specific man can become a biological father or not. However, analysis of semen can give us information about problems in the genital organs of the male and make it possible to categorize men into groups with different probabilities of achieving a pregnancy within a certain time period. Careful evaluation and preparation of semen forms an integral part of every assisted conception program. While our understanding of sperm function is increasing, decisions on whether to treat a patient are still largely based on the presence or absence of a sufficient number of motile sperm to give a preparation acceptable for in vitro fertilization. Despite several sophisticated sperm function tests, semen analysis remains the most commonly used method of assessing male fertility status.

The examination of human semen should be divided into three major parts:

1. Procedures that are considered to be minimum essential steps for semen evaluation (widely used).
2. Optional methods.
3. Sperm function tests.

For initial evaluation at least two semen samples should be collected. The interval should not be less than 7 days or more than three months. The sexual abstinence prior to semen collection should be 2-5 days.

The semen must be examined immediately after liquefaction. During initial investigation of the ejaculate, estimates of the organoleptic or macroscopic properties of the sample are determined.

This includes liquefaction, appearance, volume, consistency and pH.

1. Sperm count

Cell counts are usually performed in a Neubauer or Makler counting chamber. If the sperm number is very low or zero, the ejaculate is centrifuged and the sample from resuspended sediment is counted.

2. Other cellular elements

The ejaculate can contain polygonal epithelial cells from the urethral tract, spermatogenic cells, and leukocytes. The number of leukocytes is important because the excessive presence of these cells (leukocytospermia) may indicate the existence of reproductive tract infection, and therefore defects in semen profile such as loss of sperm function (oxidative stress).
But the difference between leukocytes and the cells of spermatogenesis is visible only after staining of the semen smear and observing them at the magnification of 600x or 1000x.

3. Grading of motility

For grading of motility, a simple grading system is recommended:

a - Rapid progressive motility;
b - Slow or sluggish progressive motility;
c - Nonprogressive motility;
d - Immotility.

In recent years, a number of new techniques for more objective assessment of the movement characteristics of human spermatozoa have been introduced such as videorecording of the semen for computer-aided analysis of sperm tracks.
With computer-aided analysis, different parameters of movement can be obtained.

4. Sperm vitality

The percentage of dead cells should not exceed the percentage of immotile cells. Such a large difference indicates structural defects in the flagellum.
Live spermatozoa are determined by either dye exclusion (Eosin-Nigrosin staining) or hypoosmotic (HOS) test. The HOS test is based on the semipermeability of the intact cell membrane, which causes spermatozoa to swell under hypoosmotic conditions. It additionally indicates integrity of the cell membrane of the sperm tail.

5. Sperm morphology

The observations on the selection of spermatozoa recovered from the female tract (cervical mucus) have helped define the appearance of a normal spermatozoon. Strict criteria should be applied when assessing the morphological normality of the spermatozoon. The head should be oval in shape (4-5.5 μ in length and 2.5-3.5 μ in width) with a well-defined acrosome region (40-70% of the head). There must be no neck, midpiece or tail defects, and no cytoplasmic droplet more than one-third the size of a normal sperm head. All borderline forms are considered abnormal. Morphological assessment should be multiparametric for each spermatozoon, hence each defect should be categorized separately.

6. Antisperm antibodies

The presence of anti-sperm antibodies (IgA, IgG) coating the spermatozoa can cause immunological infertility and agglutinations of spermatozoa. Since IgA antibodies are rarely presented without IgG antibodies, initially the MAR IgG test is recommended. Semen is mixed with latex coated with IgG. Then antihuman-IgG antiserum is added. The presence of antibodies on spermatozoa causes agglutinations between latex and spermatozoa.

7. Biochemical analysis

The health of various parts of the reproductive tract can be assessed by biochemical analysis of the ejaculate. The presence of zinc, citric acid and acid phosphatase suggest normal function of the prostate gland, and fructose and prostaglandins are specific products of the seminal vesicles. Carnitine and neutral α-glucosidase are specific products of the epididymis. However, the chemical constituents of seminal fluid have not proved particularly helpful in the treatment of male infertility.

8. Bacteriological examination

The culture of aerobic bacteria alone can be performed either on a dip slide or on blood agar by a specialized microbiology laboratory.

Volume	2-5 ml
pH	7.2 - 8
Sperm concentration	$20x10^6$ spermatozoa/ml or more
Total sperm count	$40x10^6$ spermatozoa per ejaculate or more
Motility	50% or more forward progression (a, b) or 25% rapid (a)
Morphology (Strict criteria)	5% or more ideal forms
Vitality	75% or more live (eosin staining) 85% positive HOS test
Leukocytes	Fewer than $1x10^6$/ml
MAR test	Fewer than 10% spermatozoa with adherent particles
α-Glucosidase (neutral)	20 mU or more per ejaculate
Zinc	2.4 micromol or more per ejaculate
Citric acid	52 micromol or more per ejaculate
Acid phosphatase	200 U or more per ejaculate
Fructose	13 micromol or more per ejaculate

Table 1. Normal values of semen variables and tests

9. Sperm function tests

Advanced infertility assessment in an IVF unit should include tests of sperm function. Nonacademic units are usually unable to provide a range of advanced tests. One of these tests involves sperm binding or penetration of the zona pellucida surrounding a nonviable human oocyte. The simplest sperm function test is acrosome reaction scoring. The acrosome reaction occurs on the zona pellucida after sperm binding. Its assessment is based on the counting of lectin-labeled spermatozoa using fluorescence microscopy.

Normozoospermia	Normal ejaculate
Oligozoospermia	Sperm concentration fewer than $20x10^6$/ml
Asthenozoospermia	Fewer than 50% spermatozoa with forward progression (a,b) or fewer than 25% cells of category a
Teratozoospermia (Strict criteria)	Fewer than 5% ideal forms
Oligoasthenoteratozoospermia	Disturbance of all three variables
Cryptospermia	Few spermatozoa in the ejaculate
Azoospermia	No spermatozoa in the ejaculate
Aspermia	No ejaculate

Table 2. Nomenclature for some semen variables.

GAMETES AND EMBRYOS IN VITRO

1. Culture conditions for gametes and embryos

Specific culture media (Ham F-10, Ham F-12, MEM, HTF, Earl's Balanced Salt Solution and their modifications) supplemented with amino acids, proteins, energy sources, growth factors, vitamins, antibiotics, etc. are used for the culture of oocytes, zygotes and embryos as well as for semen preparation. Oocytes, spermatozoa and different stages of embryos have various requirements, which should be taken into consideration. Because of this, more types of media have to be obtained and the pharmaceutical media manuals must be studied carefully.
The plastic dishes, in which the gametes and embryos are cultured, must be tested for embryotoxicity. The media have to be put into the dishes and covered with paraffin oil, which prevents the evaporation and contamination and maintains a more stable pH and temperature. The media should be preincubated for 24 hours in the incubator at $37^{O}C$, 95% relative humidity and 5% CO_2 before the cells are placed in.

2. Sperm preparation methods

Washing of spermatozoa to ensure the removal of seminal plasma and immotile spermatozoa is an important step in the preparation of the semen sample for IVF or intrauterine insemination (IUI). Seminal plasma contains prostaglandins and prevents fertilization, but the immotile sperm, leukocytes and cellular debris found in semen can be the source of oxidative processes. Their presence in the media with sensitive oocytes can deteriorate the culture conditions. One of the most common methods employed is washing of semen by repeated centrifugation and resuspension of sperm pellet in fresh culture medium. The main goal of the sperm preparation technique is to obtain as many motile and morphologically ideal spermatozoa from the ejaculate as possible.

3. Oocyte recovery

The human embryo culture system is based upon fixed stable parameters of temperature, pH and osmolarity. Human oocytes are very sensitive to transient cooling in vitro, and modest reductions in

temperature can cause irreversible disruption of the meiotic spindle, with possible chromosome dispersal.
A stereo dissecting microscope and heated stage is used to examine the follicular aspirates for oocytes. Each follicle is flushed with the culture medium. The aspirates and the dishes with media are kept at 37 degrees throughout. When an oocyte-cumulus complex (OCC) is found, we assess its stage of maturity by noting the density of cumulus and corona cells. The oocytes for ICSI are denuded from cumulus cells and the nuclear maturity is evaluated by observing the presence of germinal vesicle (GV) or first polar body (PB).

Immature	A tightly apposed few layers of corona and tightly packed cumulus cells surround the oocyte.
Preovulatory	The most common level of maturity seen, and most appropriate for fertilization. The cumulus is expanded into a fluffy mass. Coronal cells are still apposed to the egg.
Very mature	Little coronal material is present and it is dissociated from the egg. The cumulus is very profuse.
Luteinized	The cumulus is broken down and becomes a gelatinous mass around the egg.

Table 3. Assessment of oocyte-cumulus complex maturity.

Prophase I	The oocyte contains a germinal vesicle (GV) in the cytoplasm.
Metaphase I	The GV is not visible. There is no polar body (PB) in the perivitelline space.
Metaphase II	In the perivitelline space is a small round or fragmented first PB.

Table 4. Assessment of oocyte meiotic maturity.

4. In vitro fertilization (IVF)

The oocyte-cumulus complexes intended for the IVF procedure are washed of erythrocytes and transferred into the culture medium. The oocytes should be inseminated with previously washed 150.000 to 250.000 motile spermatozoa.

5. Intracytoplasmic sperm injection (ICSI)

When we cannot obtain enough motile spermatozoa from the ejaculate using a standard sperm washing procedure, or when we expect a failure of fertilization, a technique of mechanical union of sperm and oocyte must be used. This microsurgical technique is named intracytoplasmic sperm injection or ICSI.

Oocytes for the ICSI procedure are denuded from cumulus cells by exposure to synthetic hyaluronidase. The corona cells are mechanically removed from oocytes with a fine pipette. The denuded oocytes are transferred into drops of medium under paraffin oil. The ICSI procedure is carried out on an invert microscope, equipped with micromanipulators. The washed sperms from the ejaculate or from the testicular sample are transferred into polyvinylpyrrolidone (PVP) where they are immobilized by drawing the pipette over the tails. The sperm is then injected with the help of an injection micropipette. Penetration through the oolemma is ensured with additional ooplasm aspiration.

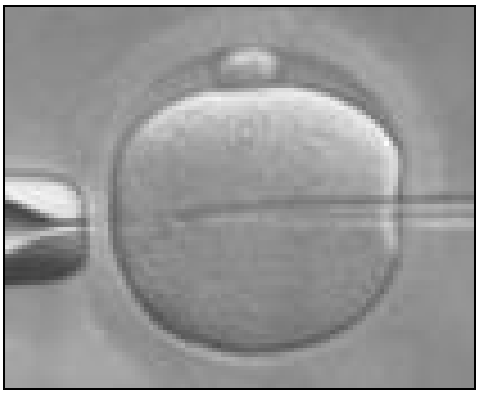


Figure 1. Intracytoplasmic sperm injection (ICSI).

6. Intracytoplasmic sperm injection with testicular sperm (TESA)

In patients with azoospermia a sample of testicular tissue is taken by aspiration biopsy (TESA) or open biopsy (TESE). A thin layer of the suspension of testicular cells is covered with paraffin oil in a petri dish. The sperm from the biopsy specimen should be found and isolated mechanically by using micromanipulator. Then a normal ICSI procedure can be performed.

7. Evaluation of fertilization

The oocytes from IVF are denuded from the corona cells 20 hours post insemination by using a fine denudation pipette. The oocytes from IVF and from ICSI are evaluated for the presence of two

pronuclei (PN), a male and female one in the ooplasm, and for the presence of the second polar body in the perivitelline space. The zygotes without PN and those with one or more than two pronuclei are not used for further clinical purposes. Two pronucleated zygotes are cultured for the next two or four days, depending on when we plan to do the embryotransfer. Different stages of embryos require various media compositions. During 5 days of cultivation the embryos must be transferred several times to new media. The embryos are evaluated every day by assessment of their morphology.

8. Assessment of early embryo morphology

Human embryos frequently do not divide properly. At each blastomere division, a number of cytoplasmic anucleated fragments of different size remain between embryonic cells. They can impede further development and hatching process. The blastomeres can also divide in two differently sized cells. The embryos also show great variations in the dynamics of division - some embryos are slow while others are rapidly dividing.
Each laboratory has different criteria for evaluation of embryo morphology. But mostly at least four morphologic categories of day 2 embryos are defined. The categories vary according to the percentage of fragments (0%, 10-20%, 20-50%, more than 50%).
In day 3 embryos, the number of blastomeres also plays a very important role in selecting the best one.

9. Assessment of blastocyst morphology

Day 5 embryos show more heterogeneous morphology than earlier stages. The most important parameters by which the blastocyst with the highest implantation potential can be selected are: expanded blastocoele, cohesive trophectoderm and particularly round shaped and compact inner cell mass.

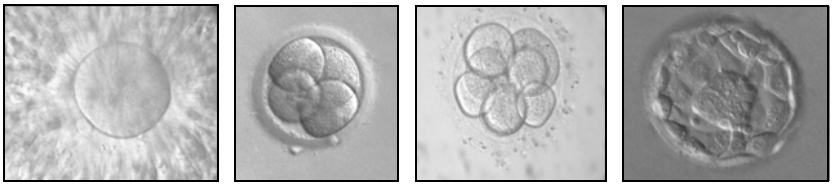


Figure 2. Early human embryo development from oocyte to blastocyst.

10. Embryos for transfer

The embryos developed in vitro have to be transferred into the uterus before day 5. In the beginnings of IVF, four or even more embryos were transferred. Because of high multiple pregnancy rates, a tendency toward decreasing the number of embryos transferred can be observed. In more developed IVF centers only two or even only one embryo is routinely transferred, but the pregnancy rate remains equally high. In such cases a very strict embryo morphology assessment is required and the culture to the blastocysts is recommended.

11. Embryo and gametes cryopreservation

Supernumerary embryos and gametes can be preserved in liquid nitrogen. Before cooling the cells have to be exposed to different cryoprotectants (propanediol, dimethyl sulphoxide, glycerol, sucrose). They cause cell dehydration and prevent the formation of intracellular ice formation. The rate of cooling varies, depending on the cell types. For controlled slow cooling a computer-controlled freezing device is required. The cells are frozen in ampoules or straws and are deposited in the container with liquid nitrogen. The thawing procedure is faster and simpler. But the cells must be exposed to decreasing concentrations of cryoprotectants before they are put in the culture medium.

12. Assisted hatching

In some cases, the zona pellucida cannot hatch. This can happen in older patients, in frozen/thawed embryos or in some unrecognized cases. Assisted hatching can be indicated in these cases and in patients with several unsuccessful IVF attempts. The process is performed by micromanipulators where a small amount of Tyrode's acid is carefully expelled on one side of the embryo. The zona starts to become thin and finally hatches. More safe is the use of a precise laser for making the opening in the zona. The same method is also used before embryo biopsy for preimplantation genetic diagnosis.

13. Preimplantation genetic diagnosis (PGD)

The embryos can be genetically analyzed for aneuploidies or for specific gene disorders. From 8-cell embryo one or two blastomeres must be biopsied by using micromanipulation methods. The blastomeres are further treated by fixation techniques for fluorescence in situ hybridization (FISH) or for polymerase chain reaction (PCR). The PGD is indicated in patients with repeated abortions and confirmed genetic diseases.

Recommended reading

1. World Health Organization. Laboratory Manual for the Examination of Human Semen and Sperm-Cervical Mucus Interaction. 2nd ed. New York: Cambridge University Press, 1992.
2. Atlas of Human Sperm Morphology. Eds. Menkveld R, Oettle EE, Kruger TF, Swanson RJ, Acosta AA, Oehninger S. Baltimore: Williams & Wilkins, 1991.
3. A Textbook of In Vitro Fertilization and Assisted Reproduction. Eds. Brisden PR, Rainsbury PA. New Jersey, USA: Parthenon Publishing, 1992.
4. Handbook of In Vitro Fertilization. 2nd ed. Eds. Trounson A, Gardner D. Portland: Book News, 1999.
5. An Atlas of Human Gametes and Conceptuses: An Ilustrated Reference for Assisted Reproductive Technology. Ed. Veeck L. Portland: Book News, 1999.

ADVANCES IN UROGYNECOLOGY

Igor But

At the beginning of the 21st century we are becoming increasingly conscious of the disorders endured by the persons affected by functional impairment of the pelvic floor and of the organs in the small pelvis, including involuntary loss of urine, feces or gas, disturbances in urogynecologic organ statics (e.g. prolapse of uterus), hemorrhoids etc. The mentioned disorders are quite frequent and are found in as many as 46.2% of women older than 15. Among the stated symptoms urinary incontinence occurs most frequently (35.3%), but often (8.8%) the symptoms are also connected with prolapse of the uterus (1).

URINARY INCONTINENCE

There are many treatment options available for the treatment of urinary incontinence (UI). In case that either pelvic floor muscle training or bladder retraining fail, *pharmacological treatment* can be offered to women with an overactive bladder as well to those women with stress UI (SUI). In the past decade substantial progress has been made in pharmacological treatment of UI. New drugs have been introduced for the treatment of an overactive bladder, especially anticholinergics (oxybutinin, tolterodine, propiverine, darifenacine, solifenacine), trospium chloride and botulinum. Studies have shown that anticholinergics are efficient and safe, however, up to 25% of patients complain about side effects (dry mouth, constipation, blurred vision...), which can ultimately lead to the discontinuation of drug use (2, 3).

Recently a new pharmacological agent was introduced for the treatment of women with stress UI - duloxetine, a selective serotonin and norepinephrine reuptake inhibitor (SNRI). Phase II and III trials found that duloxetin was associated with significant decreases in incontinence episode frequency and increased quality of life compared with placebo (4, 5).

Electrical stimulation (ES) represents another option for the treatment of urinary incontinence. ES has been reported to be effective, however, the side effects (e.g. pain, discomfort) limit the effectiveness of this treatment in many patients (6, 7). In 1999 a new method for UI treatment was introduced, namely *functional magnetic stimulation* (FMS) (8). The results of studies show that the effect of such treatment is satisfactory, and even more effective than ES in the inhibition of detrusor overactivity (8-11).

In case the above described conservative therapy does not show a satisfactory effect and in clear indications, such as urethral hypermobility accompanied by good pelvic floor muscle tonus as well as intrinsic sphincter deficiency, a surgical procedure is indicated.

Many effective surgical techniques exist for the correction of SUI. Decisions regarding the operative method are made on the basis of anatomic and urodynamic parameters in the patient. The experience of the operator is taken into consideration as well as the presence of eventual risk factors for failure of the operation and the frequency of complications accompanying individual operative methods.

It seems that tension-free support of the urethra (TVT) is very effective and represents the golden standard for operative treatment of SUI (12). It is a surgical procedure performed under local anesthesia, in which a Prolene tape is inserted under the middle part of the urethra to achieve its tension-free support. Large cohort analysis with the TVT shows a cure rate of 80% and an improvement rate of > 90% (12, 13). The complication rate is generally low, but some serious complications were described in the literature (damage to vessel, nerve or bowel). To avoid the retropubic approach and thus decrease the risk of complications, the new method of transobturator suburethral tape (MONARC, TVT-O) was developed. In this method, using the vaginal approach, the Prolene tape is inserted through the obturator membranes instead of through the retropubic space. The results of TVT-O are very promising, since the first prospective randomized study comparing TVT-O with TVT surgery showed that one year after surgery the success of TVT and TVT-O operations was comparable, 84% vs. 90%, respectively (14).

PELVIC RECONSTRUCTION SURGERY

Pelvic floor static disorders occur more frequently in advanced age and they can essentially decrease the quality of life of the affected woman. Therefore approximately every 9th woman (11.1%) decides to undergo a surgical procedure before the age of 80 (15). At Maribor Teaching Hospital (MTH) different pelvic reconstruction procedures are performed in cases of static disturbances of urogynecologic organs (e.g. uterine prolapse), vaginal hysterectomy with or without morcellation of the uterus, Manchester–Fothergill operation, anterior and posterior colporrhaphy, colpofixation to the sacrospinous ligament.

We also operate on women with fistulae (vesicovaginal, rectovaginal) and with diverticula of the urethra. We also carry out various complex and demanding endoscopic, laparoscopic procedures, while the percentage of open abdominal procedures (e.g. hysterectomies) has been lowered to a minimum, colpocystourethropexy according to Burch included.

Our surgeons acquire the necessary surgical experience abroad as well as at home, thus getting certificates for individual operative methods. As ours is a teaching center, we also issue certificates for several operations (e.g. MONARC).

Apart from educational activities, our Department is also extremely engaged in research activities. At present we are studying the significance of functional magnetic stimulation in the treatment of women with urinary incontinence and in girls with primary nocturnal enuresis.

ACKNOWLEDGMENT

The author wishes to thank Marijana Gajšek-Marchetti for her contribution in translating the present manuscript.

References

1. MacLennan AH, Taylor AW, Wilson DH, Wilson D. The prevalence of pelvic floor disorders and their relationship to gender, age, parity and mode of delivery. Br J Obstet Gynaecol 2000; 107: 1460-70.
2. Madersbacher H, Halaska M, Voight R, Allousi S, Höfner K. A placebo-controlled, multicentre study comparing the tolerability and efficacy of propiverine and oxybutinin in patients with urgency and urge incontinence. BJU International 1999; 84: 646-51.
3. Van Kerrebroeck P, Kreder K, Jonas U, Zinner N, Wein A. Tolterodine study group. Tolterodine once-daily: Superior efficacy and tolerability in the treatment of the overactive bladder. Urology 2001; 57: 414-21.
4. Norton PA, Zinner NR, Yalcin I, Bump RC. Duloxetine Urinary Incontinence Study Group. Duloxetine versus placebo in the treatment of stress urinary incontinence. Am J Obstet Gynecol 2002; 187: 40-8.
5. Dmochowski RR, Miklos JR, Norton PA, Zinner NR, Yalcin I, Bump RC. Duloxetine Urinary Incontinence Study Group. Duloxetine versus placebo for the treatment of North American women with stress urinary incontinence. J Urol 2003; 170: 1259-63.
6. Yamanishi T, Yasuda K, Sakakibara R Hattori T, Suda S. Randomized, double-blind study of electrical stimulation for urinary incontinence due to detrusor overactivity. Urology 2000; 55: 353-7.
7. Siegel SW, Richardson DA, Miller KL, Karram MM, Blackwood NB, Sand PK, at al. Pelvic floor electrical stimulation for the treatment of urge and mixed urinary incontinence in women. Urology1997; 50: 934-40.
8. Galloway NT, El-Galley RE, Sand PK, Appell RA, Russell HW, Carlan SJ. Extracorporeal magnetic innervation therapy for stress urinary incontinence. Urology1999; 53: 1108-11.
9. Galloway NT, El-Galley RE, Sand PK, Appell RA, Russell HW, Carlin SJ. Update on extracorporeal magnetic innervation (ExMI) therapy for stress urinary incontinence. Urology 2000; 56: 82-6.
10. Yamanishi T, Sakakibaba R, Uchiyama, Suda S, Hattori T, Ito H, Yasuda K. Comparative study of the effects of magnetic versus electrical stimulation on inhibition of detrusor overactivity. Urology 2000; 56: 777-81.
11. But I. Conservative treatment of female urinary incontinence with functional magnetic stimulation. Urology 2003; 61: 558-61.
12. Ward KL, Hilton P. UK and Ireland TVT Trial Group. A prospective multicenter randomized trial of tension-free vaginal tape and colposuspension for primary urodynamic stress incontinence: two-year follow-up. Am J Obstet Gynecol 2004; 190: 324-31.
13. Debodinance P, Delporte P, Engrand JB, Boulogne M. Tension-free vaginal tape (TVT) in the treatment of urinary stress incontinence: 3 years experience involving 256 operations. Eur J Obstet Gynecol Reprod Biol 2002; 105: 49-58.
14. De Tayrac R, Deffieux X, Droupy S. A prospective randomized trial comparing tension-free vaginal tape and transobturator suburethral tape for surgical treatment of stress urinary incontinence. Am J Obstet Gynecol 2004; 190: 602-8.
15. Olsen AL, Smith VJ, Bergstrom JO, Colling JC, Clark AL. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol 1997; 89: 501-6.

RESEARCH WORK AT THE DEPARTMENT OF GYNECOLOGIC AND BREAST ONCOLOGY OF MARIBOR TEACHING HOSPITAL

Iztok Takač

ABSTRACT

A comprehensive research work has been established at the Department of Gynecologic and Breast Oncology of Maribor Teaching Hospital. Among the most important recently conducted studies are a multinational study in patients with ovarian carcinoma using the HMFG1 antibody labeled with ^{90}Yttrium (R1549), (study code: SMART), a multi-national randomized Phase III GCIG Intergroup Study comparing 1st line chemotherapy with Gemcitabine, Paclitaxel and Carboplatin versus Paclitaxel and Carboplatin in previously untreated patients with epithelial ovarian cancer FIGO stages I – IV (study code OVAR-9), a multicenter phase III randomized trial comparing docetaxel in combination with doxorubicin and cyclophosphamide (TAC) versus doxorubicin and cyclophosphamide followed by docetaxel (AC→T) as adjuvant treatment of operable breast cancer Her2neu negative patients with positive axillary lymph nodes (study code BCIRG 005) and a multicenter phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC-T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC-TH) and with docetaxel, carboplatin and trastuzumab (TCH) in the adjuvant treatment of node positive and high risk node negative patients with operable breast cancer containing the her2neu alteration (study code BCIRG 006). All of these are very important multicentric and multiinstitutional studies in which several patients have been enrolled.

Key words: research, gynecologic oncology, breast

INTRODUCTION

At the Department of Gynecologic and Breast Oncology of Maribor Teaching Hospital, research work is performed by gynecologists and other practitioners involved in the diagnosis and management of gynecological cancers including vulvar, vaginal, cervical, endometrial, ovarian and breast cancers. Specific knowledge and skills are required for successful participation in the program.
In this paper only the most important multicentric studies, which have been recently performed at the Department, are presented.

1. Study SMART (28. 11. 2001 – 26. 4. 2004)

1. 1. Title

Multicenter randomized survival study of monoclonal antibody radioimmunotherapy: A multinational study in patients with ovarian carcinoma using the HMFG1 antibody labeled with ^{90}Yttrium (R1549), (Study code: SMART).

1. 2. Aim of the study

The aim of this study is to determine the efficacy and tolerability of intraperitoneally administered monoclonal antibody HMFG1 labeled with ^{90}Yttrium (R1549), in the treatment of ovarian cancer.

1. 3. Investigational drug used in the study

HMFG1 is a murine monoclonal antibody directed against the antigen known as Polymorphic Epithelial Mucin (PEM), which is expressed in over 90 % of epithelial ovarian cancer cases.

1. 4. Study design

A multinational, multicenter, randomized, parallel group comparison between HMFG1 antibody labeled with ^{90}Yttrium (R1549) and

standard treatment. The HMFG1 antibody labeled with ^{90}Yttrium will be administered once during the study, intraperitoneally.

1. 5. Study population

It is planned to include 420 eligible patients, 210 in each of the two treatment groups.
The patients must have presented originally with at least stage Ic ovarian carcinoma. They will have already been treated surgically (bilateral oophorectomy with or without salpingectomy, omentectomy and total or partial abdominal hysterectomy), and one full course of platinum-based chemotherapy. Following chemotherapy, there should be no evidence of residual or recurrent disease at second-look laparoscopy.
Prior to treatment, the following investigations will be carried out and must be within normal range or show no evidence of malignancy: clinical examination, CA 125, CT of the abdomen and pelvis, and chest X-rays.
Following the second-look laparoscopy, where there is no evidence of disease, the patients will be randomly assigned to receive either intraperitoneal radioimmunotherapy (active study medication) through a peritoneal catheter, or standard care. Where possible, if disease is found at laparoscopy and study medication has been prepared for the patient, at the discretion of the attending physician the patient may be offered treatment on a compassionate basis. The latter will not be evaluable for the main efficacy analysis. Follow-up of non-eligible patients who receive study medication will be identical to those eligible for treatment.
All patients treated with study medication will be seen weekly for 6 weeks, at 8 and 12 weeks, and 3-monthly for 36 months. Follow-up after 36 months will be at 6 monthly intervals, or more frequently if clinically warranted.
Patients randomized to the standard treatment arm will be seen at weeks 1, 4, 8 and 12 and then followed up as above.

1. 6. Study medication

Active study medication (radioimmunotherapy) for the treatment group will consist of:
25 mg of HMFG1 antibody labeled with ^{90}Yttrium (R1549) to give a dose of 666 MBq/m^2 (18 mCi/ m^2) of body surface and not greater than 1110 MBq (30 mCi) total. A free-flowing infusion of normal saline (0.9 % NaCl solution) will be set up (1 – 1.5 liters) and when half of the volume has been infused into the peritoneum, the study medication will be injected via a by-pass valve over approximately one minute.
It is important that the patient is mobilized in bed frequently during the first hour following administration of medication in order to ensure that the treatment is spread throughout the abdomen.

1. 7. Study duration

Recruitment will continue until 420 eligible patients have been recruited. In order to achieve the required power, follow-up of all patients will continue until at least 116 deaths have been observed. At present, there are limited data, which can be used to predict the pattern of survival for patients receiving standard care who satisfy the entry criteria for this study. Therefore the study duration cannot be estimated with accuracy. Consideration of several plausible scenarios suggests that average follow-up will be between 48 and 72 months.

1. 8. Assessment criteria

The main efficacy variable will be all-cause mortality. Therefore, the primary endpoint is length of survival. Length of disease-free period (relapse rate), Quality of Life assessed by the Rotterdam Symptom Checklist, ECOG Performance Status Scale, the National Cancer Institute Common Toxicity Criteria, and laboratory abnormalities and spontaneously reported adverse events will be secondary parameters for evaluation.

1. 9. Comment

The SMART study was completed on 26th April 2004. The outcomes for R1549-treated patients appeared no better than those of patients in the comparative arm of the trial. Given these findings, it is unlikely that development of R1549 will continue. A more detailed analysis of the data from SMART will be completed. The trial provides an extensive clinical database, which may be of interest for future research into ovarian cancer.

2. Study OVAR-9 (21. 2. 2002 – recruitment until 30. 6. 2004 – follow-up until 2009)

2. 1. Title

A multi-national randomized Phase III GCIG Intergroup Study comparing 1st line chemotherapy with Gemcitabine, Paclitaxel and Carboplatin versus Paclitaxel and Carboplatin in previously untreated patients with epithelial ovarian cancer FIGO stages I – IV (OVAR-9).

2. 2. Aim of the study

In ovarian cancer a platinum compound (cisplatinum or carboplatinum) is normally part of the treatment, in recent years often combined with paclitaxel (Taxol). Recent studies have shown very good responses of the tumor by adding gemcitabine to the commonly used combination of two drugs. These studies, however, were all too small to allow final conclusions on the possible efficacy of gemcitabine in combination with carboplatin and Taxol. Therefore the standard chemotherapy of ovarian cancer is still carboplatin and Taxol without gemcitabine.
The purpose of this study is to investigate if the chance for cure and for a good quality of life is improved by adding gemcitabine to the combination of carboplatin and paclitaxel (Taxol).
An international study on 1200 patients has been initiated.

2. 3. Description of the research

Patients will receive a total of 6 chemotherapy cycles given as intravenous infusion. All drugs are given on the same day, to be repeated every 21 days. Patients, who are randomized to treatment with 3 drugs, will also receive the third drug (Gemcitabine) on day 8. Patients with residual tumor after 6 cycles, but still responding to the treatment, may have 3 more cycles.
Patients will usually have a primary surgical removal of their abdominal tumor. If primary surgery is not possible, then surgery will be considered after 3 courses of chemotherapy. In some institutions patients might receive surgery even after the 6^{th} cycle.
The following tests have to be done: physical examination, blood tests, X-rays or other body scans.
After completion of the study treatment, patients will have to come for follow-up every 3 months in the first 2 years; every 6 months in years 3-5; and yearly thereafter.
Patients will be asked to complete a questionnaire before the start of treatment, after 3 cycles and after 6 cycles of chemotherapy (after cycle 9, in case of 9 cycles given) and at 6 and 12 months of follow-up.

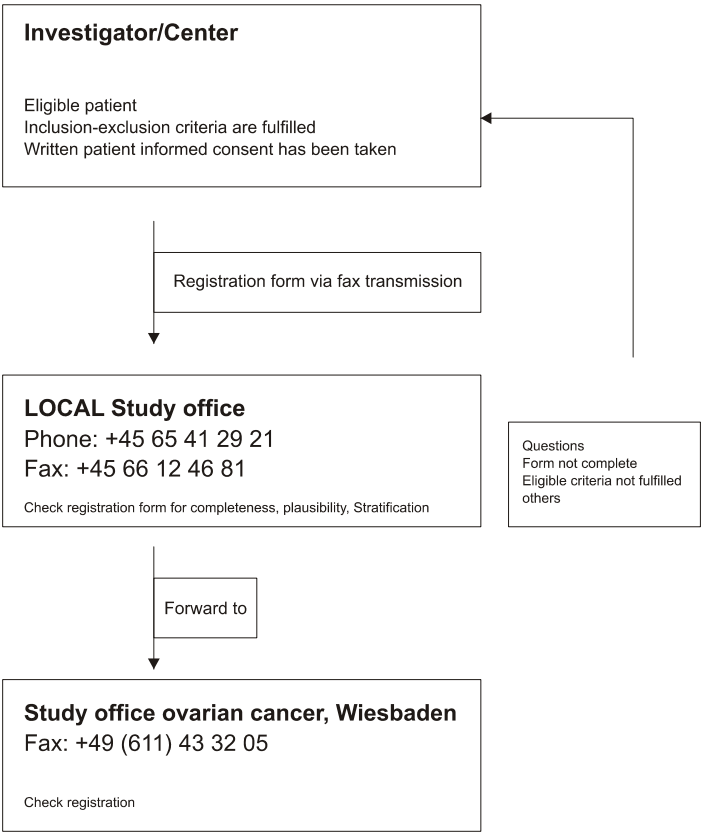
2. 4. Side effects

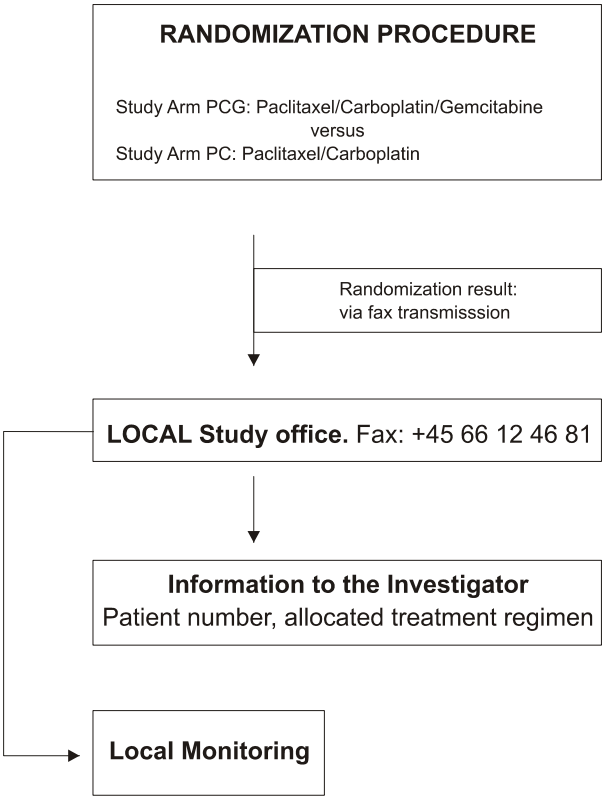
This kind of chemotherapy may cause side effects such as nausea and vomiting, which can usually be prevented by giving patients prophylactic antiemetics. Loss of hair is common, but the hair will grow out again after commencement of chemotherapy. Some degree of temporary bone marrow depression is common, leading to a decrease in the count of white blood cells, platelets and hemoglobin. As a rule this decrease is of short duration and is usually seen about 8-14 days after chemotherapy. The decrease in white blood cells may decrease the immune systems defense against infections and the decrease in platelet count may increase the risk of bleeding. Paclitaxel (Taxol) may occasionally give rise to allergic reactions. Patients will be given prophylactic medicine to prevent

this. The chemotherapy may in some cases give rise to neuropathy, presenting as numbness of fingers or toes.
The side effects that might occur as a result of surgery are: wound drainage, infection, hot flashes (in addition to other menopausal symptoms, such as thinning of the vaginal wall and decreased vaginal lubrication), possibly a shortened vagina.

2. 5. Randomization procedure

NORDIC Society for Gynecologic Oncology
Regulations are fulfilled: written confidential agreement, ethical vote center





2. 6. Serious adverse event reporting

Adverse Event Report Forms must be completed whenever a serious event occurs regardless of its causal relationship to the study drug. If only limited information is initially available, follow-up reports will be required. Thirty days after the last application of study medication, investigators should report only serious adverse events that are felt to be causally related to study drug therapy.
A Serious Adverse Event is one that meets any of the following criteria:

- Death
- Fatal or life-threatening
- Substantial or permanent disability

- Requires or prolongs hospitalization
- Cancer
- Congenital abnormality
- Overdose

Thirty days after the last application of study medication, investigators should report only serious adverse events that are felt to be causally related to study drug therapy. A copy of the SAE report should be forwarded to the appropriate Ethics Committee.
Serious adverse events must be reported immediately by the investigator via fax (using the SAE Report Form indicated for this clinical study) to the study office designated by each group.
In accordance with local law, the national authorities have to be informed by the principal investigator or his/her designee of each attending national group.
A copy of the SAE report should be forwarded to the Ethics Committee according to local law.
All reported SAEs will be forwarded via the study office designated by each group to the local pharmaceutical manufacturing companies responsible for the investigational drugs (Gemcitabine and Paclitaxel). The principal investigator of each group and the study offices designated by each group will exchange information about all occurring serious adverse events.

2. 7. Comment

The OVAR-9 study was completed on 30th June 2004. A total of 9 (nine) patients were recruited in this study from our institution. Five patients received standard treatment (TC arm) and four patients received additionally gemcitabine (TCG arm). So far, all of them are well and no relapse or progression has been observed.

3. Study BCIRG 005 (6. 3. 2001 – recruitment until 18. 2. 2003 – follow-up until 2013)

3. 1. Title

A multicenter phase III randomized trial comparing docetaxel in combination with doxorubicin and cyclophosphamide (TAC) versus

doxorubicin and cyclophosphamide followed by docetaxel (AC→T) as adjuvant treatment of operable breast cancer Her2neu negative patients with positive axillary lymph nodes.

3. 2. Aim of the study

To compare disease-free survival after treatment with docetaxel in combination with doxorubicin and cyclophosphamide (TAC) to doxorubicin and cyclophosphamide followed by docetaxel (AC→T) in operable breast cancer HER2neu negative patients with positive axillary lymph nodes. Secondary objectives were to compare overall survival between the two above-mentioned arms, to compare toxicity and quality of life between the two above-mentioned arms as well as to evaluate pathologic and molecular markers for predicting efficacy.

3. 3. Study design and dosage regimen

Prospective, non-blinded randomized phase III trial. Three thousand one hundred and thirty patients (3130) were post-surgically stratified at inclusion according to center, number of axillary lymph nodes involved (1 to 3; 4 and more) and hormonal receptor status (estrogen and/or progesterone receptor status positive versus negative). They were randomly assigned to receive either:

TAC x 6: Docetaxel 75 mg/m^2 as 1 hour IV infusion on day 1 every 3 weeks in combination with doxorubicin 50 mg/m^2 as an IV bolus and cyclophosphamide 500 mg/m^2 as IV on day 1 every 3 weeks.

AC x 4→T x 4: Doxorubicin 60 mg/m^2 as an IV bolus in combination with cyclophosphamide 600 mg/m^2 as IV followed by docetaxel 100 mg/m^2 as 1 hour IV infusion on day 1 every 3 weeks.

3. 4. Duration of treatment

All patients included in both arms received a fixed number of cycles of treatment:

- TAC x 6 cycles,
- AC x 4 cycles followed by docetaxel x 4 cycles.

3. 5. Comment

The study was completed on 18th February 2003. There were 357 centers from 38 countries participating in the study. In Slovenia 32 patients were recruited, 17 of these from our institution. Nine patients received TAC and eight patients received AC-T. Until now, one patient in the TAC arm had relapse of the disease. All other patients are well, without any signs of the disease.

4. Study BCIRG 006 (29. 1. 2001 – recruitment until 26. 3. 2004 – follow-up until 2014)

4. 1. Title

A multicenter phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC-T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC-TH) and with docetaxel, carboplatin and trastuzumab (TCH) in the adjuvant treatment of node positive and high-risk node negative patients with operable breast cancer containing the her2neu alteration.

4. 2. Aim of the study

To compare disease-free survival after treatment with doxorubicin and cyclophosphamide followed by docetaxel (Taxotere) (AC-T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (Herceptin) (AC-TH) and with docetaxel in combination with carboplatin and Herceptin (TCH) in the adjuvant treatment of node positive and high-risk node negative patients with operable breast cancer containing the HER2 alteration.

4. 3. Study design and dosage regimen

Prospective, non-blinded randomized phase III trial. Three thousand, one hundred and fifty patients (3150 patients) will be post-surgically stratified at inclusion according to institution, nodal status (node negative, node positive 1-3 nodes, node positive 4 or more nodes), of hormonal receptor status (estrogen and/or progesterone receptor

positive versus negative) and will be randomized to receive adjuvant therapy with either:

AC-T: Doxorubicin 60 mg/m^2 IV in combination with cyclophosphamide 600 mg/m^2 IV on an every 3 weeks basis for 4 cycles followed by docetaxel 100 mg/m^2 as 1 hour IV infusion on an every 3 weeks basis for 4 cycles.

AC-TH: Doxorubicin 60 mg/m^2 IV in combination with cyclophosphamide 600 mg/m^2 IV on an every 3 weeks basis for 4 cycles. Three weeks after the last cycle of AC, Herceptin 4 mg/kg loading dose by IV infusion over 90 minutes on Day 1 of Cycle 5 will be administered, followed by Herceptin 2 mg/kg by IV infusion over 30 minutes weekly starting Day 8; and docetaxel 100 mg/m^2 administered by IV infusion over 1 hour on Day 2 of Cycle 5, then on Day 1 on an every 3 weeks basis for all subsequent cycles (total 4 cycles of docetaxel). Beginning three weeks after the last cycle of chemotherapy, Herceptin 6 mg/kg by IV infusion over 30 minutes will be given every 3 weeks. Herceptin will continue for 1 year from date of first administration i.e. Herceptin administration will stop at 1 year from its initiation, regardless of the number of doses received or missed. For those cycles where docetaxel and Herceptin are due to be administered on the same day, docetaxel is to be administered first, except for the first cycle, when Herceptin loading dose is given on Day 1 and docetaxel on Day 2.

TCH: Docetaxel / Carboplatin / Herceptin: Herceptin 4 mg/kg loading dose by IV infusion over 90 minutes on Day 1 of Cycle 1 only, followed by Herceptin 2 mg/kg by IV infusion over 30 minutes weekly starting on Day 8 until three weeks after the last cycle of chemotherapy. Docetaxel 75 mg/m^2 will be administered on Day 2 of Cycle 1, then on Day 1 of all subsequent cycles by IV infusion over 1 hour followed by carboplatin at target AUC = 6 mg/mL/min administered by IV infusion over 30-60 minutes repeated every 3 weeks. A total of six cycles of
docetaxel and carboplatin will be administered every 3 weeks. Herceptin will continue weekly during treatment with chemotherapy and then every 3 weeks during the follow-up period for 1 year from date of first administration i.e. Herceptin administration will stop at 1 year from its initiation, regardless of the number of doses received or missed. During the follow-up period, Herceptin will be

administered at 6 mg/kg by IV infusion over 30 minutes every 3 weeks. For those cycles where chemotherapy and Herceptin are due to be administered on the same day, docetaxel will be administered first, followed by carboplatin followed by Herceptin except for the first cycle, when Herceptin loading dose is given on Day 1 and docetaxel/carboplatin on Day 2.
Dose reduction and/or treatment delay and treatment discontinuation are planned for the 3 arms in case of severe hematological and/or non-hematological toxicities.

Tamoxifen will be given 20 mg PO daily for 5 years, starting 3 to 4 weeks after the last course of chemotherapy for patients with positive estrogen and/or progesterone receptors unless there is a contraindication for the use of tamoxifen therapy.

4. 4. Radiation – Either Arm

Patients treated with lumpectomy will undergo postoperative radiation therapy after completion of chemotherapy and resolution of any side effect. Postmastectomy radiation therapy, and ipsilateral nodal radiation therapy, may be used at the discretion of the treating radiation oncologist. This will be done according to the guidelines at each institution.

4. 5. Comment

The study was completed on 26th March 2004. There were 429 centers from 45 countries participating in the study. In Slovenia 22 patients were recruited, among them 17 from our institution. Eight patients received TCH, five AC-T and four patients received AC-TH. Until now all other patients are well, without any signs of the disease.

CONCLUSIONS

Research work is very important for achieving the maximal quality controlled treatment of gynecologic oncology patients. It has been demonstrated that patient survival is better when patients are recruited into prospective clinical studies. Only the most important prospective, international and multiinstitutional clinical studies performed at the Department of Gynecologic and Breast Oncology of

Maribor Teaching Hospital are presented. Apart from these, research work of the Department encompasses some other national and local projects, all performed as a regular part of optimized treatment of patients with gynecologic malignancies.

References

1. Maraveyas A, Snook D, Hird V et al. Pharmacokinetics and toxicity of an Yttrium-90-CITC-DTPA-HMFG1 radioimmuno-conjugate for intraperitoneal radioimmunotherapy of ovarian cancer. Cancer 1994; 73: 1067-75.
2. Hansen SW, Anderson H, Boman K et al. Gemcitabine, carboplatin and Paclitaxel (GCP) as First-Line Treatment of Ovarian Cancer FIGO Stages IIB-IV. Proc Am Soc Clin Oncol 1999; 18: 1379.
3. Nabholtz JM. Docetaxel (Taxotere) plus doxorubicin–based combinations: the evidence of activity in breast cancer. Semin Oncol 1999; 26 (suppl. 9): 7-13.

THE STUDY
"BREAST CANCER INTERNATIONAL RESEARCH GROUP (BCIRG) 005"

Iztok Takač, Darja Arko, Robert Bali, Nina Čas Sikošek, Borut Gorišek

ABSTRACT

With the aim of evaluating the efficacy of different treatment strategies with docetaxel, doxorubicin and cyclophosphamide in adjuvant treatment of operable breast cancer patients, the international interactive Breast Cancer International Research Group (BCIRG) conducted the study BCIRG 005 (also registered as TAX GMA 301), entitled A multicenter phase III randomized trial comparing docetaxel in combination with doxorubicin and cyclophosphamide (TAC) versus doxorubicin and cyclophosphamide followed by docetaxel (AC→T) as adjuvant treatment of operable breast cancer Her2neu negative patients with positive axillary lymph nodes. The primary objective of the study is to compare disease-free survival after treatment with docetaxel in combination with doxorubicin and cyclophosphamide (TAC) to treatment with doxorubicin and cyclophosphamide followed by docetaxel (AC→T). Recruitment of patients took place from March 2000 to January 2003. During that period of time, 3134 patients from 38 countries were included in the study, among them 32 from Slovenia. Definitive results of the study will be available in the year 2013, which is 10 years after termination of recruitment.

Key words: breast cancer, study, chemotherapy, antracyclines, taxanes

INTRODUCTION

Breast cancer is the most frequent cancer in women, comprising 24 % of all female cancers. It is also the most common cause of death in women due to malignancy. In the year 1999 there were 999 new cases of breast cancer in Slovenia, giving an incidence of 97.8 per 100.000 women (1).

Breast cancer patients are most frequently treated with a combination of surgery, radiotherapy, chemotherapy and hormonal treatment (2). Despite all treatment efforts, a significant proportion of breast cancer patients still die due to distant metastases, which are more frequent in patients with positive lymph nodes (3). Adjuvant treatment with chemotherapy and hormonal therapy reduces mortality by about a third.

Abnormal expression of human epidermal growth factor receptor 2 (HER2) is frequently observed in a number of primary human tumors, suggesting that the overexpression of this growth factor receptor may contribute to transformation and tumorigenesis. In most of these cases, pathologic HER2 protein overexpression is thought to result from gene amplification and has been correlated with poor clinical outcome in patients with both breast and ovarian cancers. Approximately 25 % to 30 % of patients with breast and 8-11 % of ovarian cancers overexpress HER2.

A number of chemotherapy protocols have shown effectiveness in the adjuvant setting of breast cancer. The most optimal regimen has not yet been identified. Several regimens represent acceptable alternatives. They range from CMF chemotherapy of variations to anthracycline- containing regimens such as AC, CAF, FAC, AVCF or FEC. The impact of antracycline-containing polychemotherapy appears real, but modest when compared to other regimens in the adjuvant setting. Overall, in both node-negative and node-positive patients, adjuvant chemotherapy significantly improves disease-free and overall survival in young patients and to a lesser extent in older patients. Among the novel chemotherapeutic drugs introduced in the 1990's, the taxanes have emerged as the most powerful compounds and the available results suggest that they will be remembered in the future as the breast cancer chemotherapy of the 1990's (4, 5, 6).

Taxotere is the leading compound of the new class of cancer agents called taxanes, which are confirmed as the most important entry in breast cancer therapy over the last two decades. In 1999, the first

generation of adjuvant trials comparing taxane-antracycline-containing combinations to classical anthracycline-containing polychemotherapy were either completed or nearing completion. The trend was to open the second generation of adjuvant trials with taxanes, in which both arms contain taxanes.
One of the main questions in the adjuvant setting is related to the direct comparison of both strategies (sequence vs. polychemotherapy).
With the aim to determine a potential optimal polychemotherapy, the Breast Cancer International Research Group (BCIRG) proposed a trial comparing 6 courses of docetaxel in combination with doxorubicin and cyclophosphamide (TAC) to doxorubicin and cyclophosphamide followed by docetaxel (AC→T) in operable breast cancer HER2neu negative patients with positive axillary lymph nodes. The study was entitled "A multicenter phase III randomized trial comparing docetaxel in combination with doxorubicin and cyclophosphamide (TAC) versus doxorubicin and cyclophosphamide followed by docetaxel (AC→T) as adjuvant treatment of operable breast cancer HER2neu negative patients with positive axillary lymph nodes."

Primary objective

To compare disease-free survival after treatment with docetaxel in combination with doxorubicin and cyclophosphamide (TAC) to doxorubicin and cyclophosphamide followed by docetaxel (AC→T) in operable breast cancer HER2neu negative patients with positive axillary lymph nodes.

Secondary objectives

To compare overall survival between the 2 arms mentioned above.
To compare toxicity and quality of life between the 2 arms mentioned above.
To evaluate the pathologic and molecular markers for predicting efficacy.

Study design and dosage regimen

A prospective, non-blinded randomized phase III trial. Three thousand one hundred and thirty patients (3130) were post-surgically stratified at inclusion according to center, number of axillary lymph

nodes involved (1 to 3; 4 and more) and hormonal receptor status (estrogen and/or progesterone receptor status positive versus negative). They were randomly assigned to receive either:

TAC x 6:
Docetaxel 75 mg/m^2 as 1 hour IV infusion on day 1 every 3 weeks in combination with doxorubicin 50 mg/m^2 as an IV bolus and cyclophosphamide 500 mg/m^2 as IV on day 1 every 3 weeks.
(Sequence of administration: doxorubicin followed by cyclophosphamide followed by docetaxel).

AC x 4→T x 4:
Doxorubicin 60 mg/m^2 as an IV bolus in combination with cyclophosphamide 600 mg/m^2 as IV followed by docetaxel 100 mg/m^2 as 1 hour IV infusion on day 1 every 3 weeks.

Dose reduction and/or treatment delay and treatment discontinuation are planned for the 2 arms in case of severe hematological and/or non-hematological toxicities.

Indication for tamoxifen – either arm
Tamoxifen 20 mg PO daily for 5 years, starting 3 to 4 weeks after the last course of chemotherapy for patients with positive estrogen and/or progesterone receptors unless there is a contraindication for the use of tamoxifen therapy.

Indication for radiation – either arm
Patients treated with lumpectomy underwent postoperative radiation therapy after completion of chemotherapy and resolution of any side effects. Postmastectomy radiation therapy, and ipsilateral nodal radiation therapy, may be used at the discretion of the treating radiation oncologist. This will be done according to the guidelines at each institution. The guidelines for postoperative radiation therapy per institution have been collected.

Prophylactic premedication regimen
Patients receiving docetaxel in the TAC arm or docetaxel in the AC→T arm have been receiving the following prophylactic premedication:

- Dexamethasone (8 mg) or methylprednisolone (40 mg) or prednisone (50 mg) or prednisolone (50 mg) PO for 6 doses:
  1. The night before docetaxel,
  2. The morning of docetaxel,
  3. One hour before docetaxel infusion,
  4. The night of docetaxel chemotherapy,
  5. The morning of the day after docetaxel chemotherapy,
  6. The evening of the day after docetaxel chemotherapy.

Prophylactic antibiotic (TAC arm only):
- Ciprofloxacin 500 mg PO twice a day for 10 days starting on day 5 of each cycle.

Number of patients/enrolment period/follow-up period

Number of patients:	3130 (1565 patients per arm)
Enrolment start:	August 2000
Enrolment stop:	January 7, 2003
Clinical follow-up:	10 years
First follow-up analysis:	2011
Second follow-up analysis:	2013

Duration of treatment

All patients included in both arms received a fixed number of treatment cycles:
- TAC x 6 cycles,
- AC x 4 cycles followed by docetaxel x 4 cycles.

SELECTION OF PATIENTS

Inclusion criteria

1. Written informed consent prior to beginning specific protocol procedures, including expected cooperation of the patients for the treatment and follow-up, must be obtained and documented according to the local regulatory requirements.
2. Histologically proven breast cancer. The interval between definitive surgery that includes axillary lymph node dissection and registration is less than or equal to 60 days. A central pathology review may be performed post randomization for

confirmation of diagnosis and molecular studies. The same block used for HER2neu determination prior to randomization may be used for the central pathology review.

3. Definitive surgical treatment must be either mastectomy, or breast conserving surgery with axillary lymph node dissection for operable breast cancer (T1-3, clinical N0-1, M0). Margins of resected specimen from definitive surgery must be histologically free of invasive adenocarcinoma and ductal carcinoma in situ (DCIS). Lobular carcinoma in situ does not count as a positive margin.
4. Histological examination of the tumor: invasive adenocarcinoma with at least one axillary lymph node (pN1) showing evidence of tumor among a minimum of six resected lymph nodes.
5. The tumor must show negative HER2neu proto-oncogene overexpression by FISH. Confirmation of negative overexpression is centrally assessed by an authorized BCIRG laboratory prior to randomization using a paraffin block.
6. Estrogen and/or progesterone receptor analysis performed on the primary tumor prior to randomization. Results must be known at the time of randomization.
7. Age $\geq$ 18 years and age $\leq$ 70 years. The upper age limit is not meant to be exclusionary but rather is based on the lack of safety data for the TAC regimen for women > 70 years of age.
8. Karnofsky Performance status index $\geq$ 80 %.
9. Normal cardiac function must be confirmed by LVEF (MUGA or echocardiography) and ECG within 3 months prior to registration. LVEF must be above or equal to the lower limit of normal for the institution. The ECG results must be within normal limits or show no significant abnormalities.
10. Laboratory requirements (within 14 days prior to registration):
    a) Hematology:
        - Neutrophils $\geq 2.0 \times 10^9$/L,
        - Platelets $\geq 100 \times 10^9$/L,
        - Hemoglobin $\geq$ 10 g/dL;
    b) Hepatic function:
        - Total bilirubin $\leq$ 1 UNL,
        - ASAT (SGOT) and ALAT (SGPT) $\leq$ 2.5 UNL,
        - Alkaline phosphatase $\leq$ 5 UNL,
        - Patients with ASAT and/or ALAT >1.5 x UNL associated with alkaline phosphatase are not eligible for the study;

c) Renal function:
   - Creatinine $\leq$ 175 μmol/L,
     is the limit reached, the calculated creatinine clearance should be $\geq$ 60 mL/min.

11. Complete staging work-up within 3 months prior to registration. All patients had contralateral mammography, chest X-ray (PA and lateral) and/or CT scan and/or MRI, abdominal ultrasound and/or CT and/or MRI, and bone scan. In case of a positive bone scan, bone X-ray is mandatory to rule out the possibility of non-metastatic hot spots. Other tests may have been performed as clinically indicated.
12. Patients must be accessible for treatment and follow-up. The patients registered for this trial must have been treated and followed at the participating center, which could be the principal or co-investigator's site.
13. Negative pregnancy test (urine or serum) within 7 days prior to registration for all women of childbearing potential.

Exclusion criteria

1. Prior systemic anticancer therapy for breast cancer (immunotherapy, hormone therapy, gene therapy, chemotherapy).
2. Prior anthracycline therapy or taxoids (paclitaxel, docetaxel …) for any malignancy.
3. Prior radiation therapy for breast cancer.
4. Bilateral invasive breast cancer.
5. Pregnant or lactating patients. Patients of childbearing potential must implement adequate non-hormonal contraceptive measures during study treatment (chemotherapy and tamoxifen therapy) and must have negative urine or serum pregnancy test within 7 days prior to registration.
6. Any T4 or N2 or known N3 or M1 breast cancer.
7. Pre-existing motor or sensory neurotoxicity of a severity $\geq$ grade 2 by NCI-CTC, version 2.0.
8. Other serious illness or medical condition:
   a) Congestive heart failure or unstable angina pectoris, previous history of myocardial infarction within one year from study entry, uncontrolled hypertension or high-risk uncontrolled arrhythmias.
   b) History of significant neurologic or psychiatric disorders including psychotic disorders, dementia or seizures that

would prohibit the understanding and giving of informed consent.
   c) Active uncontrolled infection.
   d) Active peptic ulcer, unstable diabetes, unstable diabetes mellitus.
9. Past or current history of neoplasm other than breast carcinoma, except for:
   a) Curatively treated non-melanoma skin cancer.
   b) Carcinoma in situ of the cervix.
   c) Other cancer treated curatively and no evidence of disease for at least 10 years.
   d) Ipsilateral ductal carcinoma in situ (DCIS) of the breast.
   e) Lobular carcinoma in situ (LCIS) of the breast.
10. Chronic treatment with corticosteroids unless initiated > 6 months prior to study entry and
    at low dose (≤ 20 mg methylprednisolone or equivalent).
11. Concurrent treatment with ovarian hormonal replacement therapy. Prior treatment should be stopped before study entry.
12. Definite contraindications for the use of corticosteroids.
13. Concurrent treatment with other experimental drugs. Participation in another clinical trial with any investigational not marketed drug within 30 days prior to study entry.
14. Concurrent treatment with any other anti-cancer therapy.
15. Male patients, as no clinical efficacy of safety data are available from phase I-II studies.
16. Current therapy with any hormonal agent such as raloxifene, tamoxifen or other selective estrogen receptor modulators (SERMs), either for osteoporosis or prevention. Patients must have discontinued these agents prior to randomization.

EFFICACY EVALUATION

- An intent-to-treat (ITT) analysis will be conducted for all randomized patients. In addition, an analysis will be conducted among the eligible patients.

- Disease-Free Survival (DFS) is defined as the interval from the date of randomization to the date of local, regional or metastatic relapse or the date of second primary cancer (with the exception of curatively treated non-melanoma skin cancer or

carcinoma in situ of the cervix – see Exclusion criteria 9a, 9b) or death from any cause whichever occurs first.

- Survival will be measured from the date of randomization up to the date of death of any cause.

SAMPLE SIZE DETERMINATION

The primary objective of this trial is to show that TAC differs from AC-T in terms of disease free survival (DFS). The following assumptions are made:

- The DFS at 5 years for node-positive patients receiving AC-T is around 50%.
- It is of clinical interest to detect a 5% improvement in 5-year DFS i.e. an increase from 50% to 55%.
- The error rate for a false positive outcome (a) is set to 5%, using two-sided significance tests.
- The error rate for a false negative outcome (b) is set to 20% i.e. the power of the trial is set to 80% for the difference of clinical interest.

A sample of 3130 patients (1565 patients per treatment arm) is necessary, assuming 3% of patients will be found ineligible after randomization.
The treatment assignment will be based on a dynamic minimization procedure using center, number of axillary lymph nodes involved (1 to 3, 4 and more), hormonal receptor status (estrogen and/or progesterone receptor positive versus negative), as factors in the minimization algorithm, which will use a stochastic treatment allocation based on the variance method.
The sample size means that the trial is powered to detect a 5% difference between the two treatment arms, assuming the 5-year DFS in the control group is 50% (i.e. a 14% reduction in relative risk). In case the DFS in the control arm is > 50%, a 5% absolute difference in DFS will still be detectable.
This sample size calculation takes into account the fact that one interim analysis will be performed after 50% of the expected events have been observed. The main analysis will take place 5 years after recruitment of the last patient into the trial. A total of 1488 events

are required among all patients at the time of the final analysis. Two confirmatory analyses will be performed at 8 years and finally at 10 years after recruitment of the last patient into the trial. The purpose of these follow-up analyses is to update the DFS and OS estimates. All randomized patients will be followed until death or until 10 years after the last patient entry.
With the sample size as stated in the primary endpoint, this trial has 80% power (at a 0.05 significance level) to detect an absolute difference in overall survival of approximately 5%. If overall survival (at 5 years) in the control arm is between 70% and 80%, the detectable difference in the experimental arm is between 4.5% and 3.9%, respectively. This translates into detecting a relative risk between 18% and 22%.
A pragmatic group sequential design, as suggested by Haybittle-Peto, will be used with a significance level of 0.001 for the interim analysis. This allows for the use of an unadjusted level of 0.05 for the final analysis.

CONCLUSIONS

Until February 18, 2003, when enrollment closed, 3301 patients were enrolled. Participating in the study were 357 centers from 38 countries. Recruiting countries with 0 to 9 patients were Saudi Arabia, Portugal, Estonia, Uruguay, Cyprus, Mexico, Greece, Egypt and Hong Kong. Bosnia, Venezuela and Columbia recruited 10 to 20 patients; the Czech Republic and Bulgaria 20 to 30 patients; Slovenia, Taiwan, Romania, France and China 30 to 39 patients (Slovenia: Ljubljana 15 patients, Maribor 17 patients); South Africa, Brazil, Lebanon, Korea, Croatia, Argentina, Belgium, Russia, Spain and Hungary 40 to 99 patients, Israel and Ireland 100 to 199 patients; Poland, Australia, New Zealand and Canada recruited 300 to 399 patients. Germany recruited around 450 patients and the USA approximately 570 patients.

Until June 30, 2004, all CRF's of baseline, cycles and EOC (100 %) were collected. Meanwhile 67 % of FUP forms had already been collected. A total of 1327 patients had been reviewed for eligibility. There is no concern among the patients reviewed. A total of 1200 patients was validated by the central study management team.

The efficacy analysis is planned for Q1 2006, when 744 events should be observed (breast cancer relapse, 2nd primary malignancy, death). The final efficacy analysis is planned for Q1 2008, when 1488 events should be observed.
Until June 30, 2004, 1106 serious adverse events were reported. Toxicity is predominantly hematological, representing 67 % of the adverse drug reactions. The number of cases of various toxicities were as follows: infection/febrile neutropenia (675), blood/bone marrow (135), gastrointestinal (120), cardiovascular (43), dermatology/skin (33), constitutional symptoms (27), pain (15), neurology (14), pulmonary (9), allergy (7), genito/urinary (6), hemorrhage (5), peripheral edema (4), hepatic (3), metabolic (1), and other (9).
Six fatal cases related to chemotherapy occurred:

- Two during the study treatment/observation period:
  - One death due to hepatic failure was reported in a Hepatitis B carrier patient,
  - One death due to septic shock (a pleural effusion and hemothorax due to central venous catheter implantation are confounding factors that may have contributed to the fatal outcome)
- Four delayed toxicities:
  - Two deaths due to acute myeloid leukemia/myelodysplastic syndrome,
  - Two deaths due to respiratory insufficiency (one secondary to a congestive heart failure).

References

1. Pompe Kirn V, Golouh R, Lindtner J et al. (ur). *Incidenca raka v Sloveniji 1999.* Ljubljana: Onkološki inštitut; 2002: 13-44.
2. Osborne CK, Clark GM, Ravdin PM. Adjuvant systemic therapy of primary breast cancer. In: Harris JR, Lippman ME, Morrow M, Hellman S (eds). Disease of the breast. Lippincot–Raven, Philadelphia, New York, 1996: 548.
3. National Cancer Institute of Canada: Canadian cancer statistics 1996; Toronto, Canada, 1996; 21-3.
4. Nabholtz JM. Docetaxel (Taxotere) plus doxorubicin–based combinations: the evidence of activity in breast cancer. Semin Oncol 1999; 26 (suppl. 9): 7-13.
5. Dieras V. Docetaxel in combination with doxorubicin: a phase I dose-finding study. Oncology 1997; 6 (suppl. 6): 17-20.
6. Chan S, Friedrichs K, Noel D et al. Prospective randomised trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. J Clin Oncol 1999; 17: 2341-54.

MOLECULAR CYTOGENETIC DIAGNOSTICS IN OBSTETRICS AND GYNECOLOGY

Nadja Kokalj Vokač

INTRODUCTION

Although karyotyping remains the golden standard of chromosome analysis and still is the most frequently used genetic method in prenatal and postnatal diagnosis, the most important advance in cytogenetics over the past two decades in clinical genetics laboratories are molecular cytogenetic techniques. The pioneer among them was fluorescence in situ hybridization (FISH), which allows the identification of specific sequences in a structurally preserved cell, in metaphase or interphase. Different FISH technologies provide increased resolution for the elucidation of structural chromosome abnormalities that cannot be resolved by more conventional cytogenetic analysis, including microdeletion syndromes, cryptic or subtle duplications and deletions, complex rearrangements involving many chromosomes, and marker chromosomes. Interphase FISH is used for the rapid prenatal and preimplantation diagnosis of selected aneuploidies, and determining the amplification of oncogenes associated with specific forms of cancer and neoplasia.

FISH – PRINCIPLES

The technique of fluorescence in situ hybridization relies on the unique ability of a portion of single-stranded DNA, known as a probe, to anneal (hybridize) with its complementary target DNA sequence, wherever it is located in the genome. The probe is visualized either directly by the incorporation of a fluorochrome-conjugated nucleotide label or indirectly with the incorporation of a reporter molecule (biotin-dUTP or dioxigenin –dUTP), which is released in a

follow-up step. Target sequences of probes can be either metaphase or interphase chromosomes.

There are three categories of chromosome specific probes, each offering different applications: repetitive probes, painting probes and locus specific probes. Most commonly used repeated sequences are centromeric specific satellite probes, which are used for chromosome enumeration and aneuploidy detection. Painting probes are labeled collections of specific DNA sequences that span part of, or the entire length of, an individual chromosome. Chromosome painting can be particularly useful in chromosome analysis of cancer where individual chromosomes may undergo complex rearrangements. Additionally, this technique is useful for detecting supernumerary marker chromosomes. A locus specific probe is capable of annealing to a single gene locus that ranges in size from less than 1000 bp to as many as 1000000 bp. Locus specific probes can be used to localize a gene to a chromosome region or to determine whether deletions and duplications at the submicroscopic level are present.

M-FISH (Multicolor)

The technique of multicolor-FISH derives from the original technology of whole chromosome painting probes and takes advantage of the simultaneous visualization of multiple targets using combinatorial labeling. Using combinatorial labeling with five or more fluorochromes results in a unique color presentation for each one. With the application of this approach, simultaneous detection of all 24 human chromosomes in individual cells is possible. M-FISH has been evaluated for use in the identification of markers, derivative chromosomes and complex karyotypes in products of conception, amniocytes and blood cultures. There are limitations to M-FISH, which include the inability to detect intrachromosomal inversions, insertions or subtle deletions and duplications (1, 2, 3).

CGH (Comparative Genome Hybridization)

CGH is a robust FISH method for assessing the entire genome. CGH provides the means for a comprehensive analysis of the copy number, i.e. gain or loss of chromosome material. The advantage of the method is that no dividing cells are needed. The application in obstetrical genetics has been limited at present. Balanced structural rearrangements, such as translocations or inversions, go undetected

with CGH. CGH has been successfully applied in the genomic analysis of products of conception. The rationale for using CGH in this instance was based on the fact that frequently tissues derived from abortions fail to grow in culture. CGH has been applied to single blastomeres in efforts to provide a complete chromosome analysis of preimplantation embryos (4, 5).

CLINICAL APPLICATIONS OF FISH

Interphase FISH in prenatal diagnosis

Both repetitive and locus specific probes may be used to determine chromosome number for the most clinically important aneuploid status: autosomal trisomies for chromosomes 13, 18, 21 and the X and Y sex chromosomes. Cell culture is not required prior to analysis and therefore the technique has been used to provide rapid identification of aneuploidy within 6-8 hours of sampling. Interphase FISH analysis has been successfully applied in prenatal and genetic diagnosis of chromosome aberration in uncultured or short-term cultured amniocytes and chorionic villus cells (6, 7, 8).

Other clinical applications of FISH in prenatal diagnosis

Locus specific and painting probes have been used in diagnosing microdeletion syndromes, marker chromosomes, and chromosome mosaicism. Like microdeletions, cryptic translocations are by definition chromosome rearrangements not visible by conventional karyotyping; these frequently involve subtelomeric regions of chromosomes. Unbalanced translocations not visible by conventional karyotyping have been associated with congenital malformations and mental retardation. It has been estimated, for example, that 6-8% of unexplained mental retardations are caused by cryptic subtelomeric unbalanced rearrangements. Since such arrangements may be present in the cells of parents who are balanced carriers, their identification is essential if prenatal diagnosis in future pregnancies is to be undertaken (9).

The identification of marker chromosomes during prenatal chromosome analysis raises serious concern regarding the phenotypic consequences to the fetus and can create difficult counseling problems. The small chromosome markers (SMC – supernumerary marker chromosomes) are structurally abnormal and cannot be

identified with conventional chromosome banding techniques. The most common group of marker chromosomes involves only the paracentromeric region of a chromosome, often with satellites at one or both ends. As has been shown about 80% are derived from acrocentric chromosomes. Many of these are either pseudo idic (15), also called inverted duplication, inv dul (15), or SMC derived from chromosome 22. When the inv dup (15) includes the Prader-Willi/Angelman critical region, it is associated with mild to severe mental retardation. About 40% of SMC found on prenatal analysis are inherited, and the risk of an adverse phenotype in the fetus is usually low if the carrier parent has a normal clinical phenotype. A review of de novo cases of non-acrocentric, autosomal SMC characterized by FISH gave a risk estimate of an abnormal phenotype of about 28%. The unequivocal identification of the origin and composition of SMC is clearly crucial for karyotype – phenotype correlation and a more accurate assessment of risk in individual cases. For detection of SMC, multicolor FISH (M-FISH), or cenM-FISH, using differently colored all human centromeres, are particularly helpful techniques (10, 11, 12).

Preimplantation genetic diagnosis

The major cause of pregnancy failure following in vitro fertilization (IVF) and embryo transfer is a chromosome aberration. Using FISH analysis for five chromosomes 13, 18, 21, X and Y, estimation of clinically important numerical aberrations in fertilized oocytes and preimplantation embryos is possible. This approach is being applied particularly to women of advanced age, 37 and older, since this group has significantly lower pregnancy rates following IVF compared to their younger counterparts. For parents at high reproductive risk for chromosomally unbalanced gametes because they carry structural rearrangements, such as reciprocal translocations, preimplantation genetic diagnosis offers the opportunity to enhance pregnancy outcomes. By using a combination of subtelomeric probes combined with proximal probes, it is possible to identify all possible segregation products in parents who are balanced translocation carriers (13, 14, 15).

References

1. Speicher MR, Ballard SG, Ward DC. Karyotyping human chromosomes by combinatorial multi-fluor FISH. Nature Genetics1996; 12: 368-75.
2. Schrock E, du Manoir S, Veldman T et al. Multicolor spectral karyotyping of human chromosomes. Science 1996; 273: 494-7.
3. Jalal SM, Law ME. Utility of multicolor fluorescent in situ hybridization in clinical cytogenetics. Genetics in Medicine 1999; 1: 181-6.
4. Daniely M, Barkai G, Goldman B, Aviram–Goldring A. Detection of numerical chromosome aberrations by comparative genomic hybridization. Prenatal Diagnosis 1999; 19: 100-4.
5. Wells D, Sherlock JK, Handysisde AH, Delhanty JD. Detailed chromosomal and molecular genetic analysis of single cells by whole genome amplification and comparative genomic hybridization. Nucleic Acids Research 1999; 27: 1214-8.
6. Eiben B, Trawicki W, Hammans W et al. Rapid prenatal diagnosis of aneuploidies in uncultured amniocytes by fluorescence in situ hybridization. Evaluation of >3000 cases. Fetal Diagnosis and Therapy 1999; 14: 193-7.
7. Pergament E, Chen PX, Thangavelu M, Fiddler M. The clinical application of interphase FISH in prenatal diagnosis. Prenatal Diagnosis 2000; 20: 215-20.
8. Evans MI, Henry GP, Miller WH et al. International collaborative assessment of 146 000 prenatal karyotypes: expected limitations if only chromosome-specific probes and fluorescence in-situ hybridization is used. Hum Reproduction 1999; 14: 1213-6.
9. Flint J, Wilkie AOM, Buckel VJ et al. The detection of subtelomeric chromosomal rearrangements in idiopathic mental retardation. Nature Genet 1995; 9: 132-40.
10. Plattner R, Heerema NA, Howard-PabBles PN et al. Clinical findings in patients with marker chromosomes identified by fluorescence in situ hybridization. Hum Genet 1993; 91: 589-98.
11. Crolla JA, Harvey JF, Stitch FL, Dennis NR. Supernumerary marker 15 chromosomes: a clinical, molecular and FISH approach to diagnosis and prognosis. Hum Genet 1995; 95: 161-70.
12. Crolla JA, Long F, Rivera H, Dennis NR. FISH and molecular study of autosomal supernumerary marker chromosomes excluding those derived from chromosome 15 and 22. Results of 26 new cases. Am J Med Genet 1998; 75: 355-66.
13. Delhanty JD. Chromosome analysis by FISH in human preimplantation genetics. Human Reproduction 1997; 12: 153-5.
14. Munne S, Magli C, Cohen J et al. Positive outcome after preimplantation diagnosis of aneuploidy in human embryos. Human Reproduction 1999; 14: 2192-9.
15. Scriven PN, Handysisde AH, Ogilvie CM. Chromosome translocations: segregation modes and strategies for preimplantation genetic diagnosis. Prenatal Diagnosis 1998; 18: 1437-49.

TRANSVAGINAL SONOGRAPHIC EVALUATION IN CLINICAL SUSPICION OF INCOMPETENT CERVIX DURING PREGNANCY

Marijan Lužnik

ABSTRACT

Background: With transvaginal sonographic cervical evaluation we attempted to objectify anatomic changes of the cervix in pregnant women with clinical suspicion of incompetence in the second trimester of pregnancy.
Methods: In a group of 112 singleton-pregnant women with clinical suspicion of incompetent cervix or with a history of premature birth in previous pregnancies, US evaluation of cervical length and of the shape of the internal cervical os was performed. On the basis of repeated hospital gynecological examinations, the patients were divided in two groups: a study group of 57 women with cervical incompetence and a control group of 55 women with competent cervix. In all cases cervical evaluation was performed by transvaginal sonographic measurement of cervical length and of eventual changes of the internal cervical os.
Results: In 57 of 112 women clinical evaluation of the cervix revealed a length of 1 cm or less. In this clinically suspicious group, the measured cervical length was between 11 mm and 52 mm, the calculated mean cervical length was 29.2 mm and standard deviation 8.59. Dilatation of the internal cervical os exceeding 5 mm was found in 22 of 57 cases.
In the control group of 55 women, the measured cervical length was between 21 mm and 50 mm, the calculated mean cervical length was 36.5 mm and standard deviation 6.87. Dilatation of the internal cervical os exceeding 5 mm was found in 5 cases.
Conclusion: In more than half of the cases in our study group, cervical length values were unexpectedly high for an incompetent cervix. This was also reflected by the low percentage of (at least minimal) changes of the internal cervical os shape, which was found in 39% (22/57).

Key words: transvaginal sonography, cervical incompetence, pregnancy, clinical examination, comparison

INTRODUCTION

The cervix uteri is very important for pregnancy as well as birth. It enables the pregnancy to continue for the proper time and finally it permits a delivery with dilatation of the cervical canal (1). Shortening of the cervix and preterm dilatation were recognized early as risk factors for prematurity (2 - 6).

Cervical insufficiency, or an incompetent cervix, is exhibited by prolapse of fetal membranes or protruding of membranes into the vagina due to painless cervical dilatation in the mid- or early third trimester, followed by preterm premature rupture of membranes (PPROM) and preterm delivery (7, 8).

Clinically the cervix is assessed by inspection with a speculum and by palpation of its vaginal part. The supravaginal part of the cervix is palpable only through the fornices of the vagina.

METHODS

One hundred twelve singleton-pregnant women at risk of cervical incompetence (cases after cervical cone biopsy were not included) were included in the prospective study group. In 1977 they were referred by their personal gynecologist to the Department of Gynecology and Obstetrics of General Hospital Slovenj Gradec because of clinical examination findings suspect of cervical incompetence, or/and because of a history of premature birth in previous pregnancies. On the basis of repeated hospital gynecological examinations, the group was divided in two groups: a study group of 57 women with cervical incompetence and a control group of 55 women with competent cervix. In all cases cervical evaluation was performed by transvaginal sonographic measurement of cervical length and of the shape of the internal cervical os between the 18^{th} and 23^{rd} week of pregnancy. Vaginal sonography was performed by the principal investigator with a Kretz Combison 320-5 US scanner with a 240° view angle and using a 5 or 7.5 MHz vaginal transducer. After she emptied her bladder, the patient was examined in the dorsal lithotomy position. The vaginal probe was covered with a sterile condom. The cervical length was measured along the endocervical canal from the internal to the external os

(Fig. 1.A.). Additional assessment of the internal os was made with a transfundal pressure maneuver and an eventual funneling change was measured and documented for statistic evaluation (Fig. 1.B.).

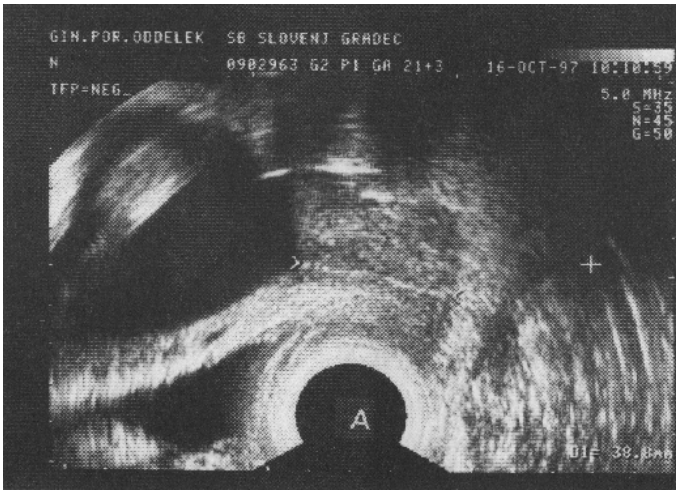


Fig. 1.A. Measurement of cervical length by transvaginal sonography in a normal cervix.

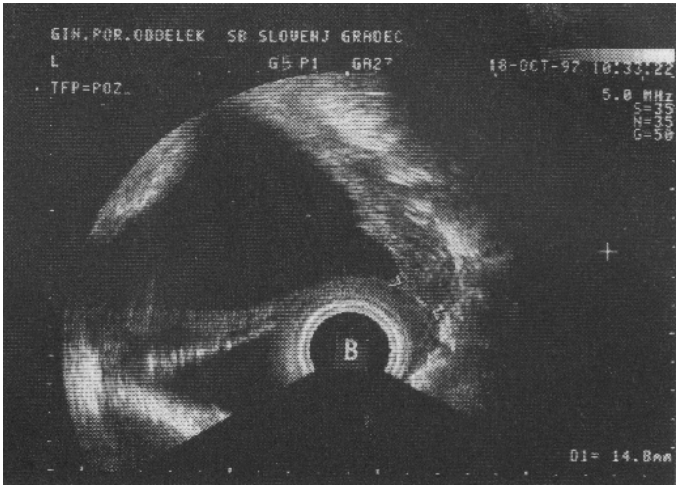


Fig. 1.B. Measurement of cervical length by transvaginal sonography in severe shortening and marked funneling of the cervix.

RESULTS

In 57 of 112 women, clinical evaluation of the cervix length was 1 cm or less. In this clinically suspicious group, the measured cervical length was between 11 mm and 52 mm, the calculated mean cervical length was 29.2 mm and standard deviation 8.59. Dilatation of the internal cervical os exceeding 5 mm was found in 22 of 57 cases.

In the control group of 55 women, the measured cervical length was between 21 mm and 50 mm, the calculated mean cervical length was 36.5 mm and standard deviation 6.87. Dilatation of the internal cervical os exceeding 5 mm was found in 5 cases.

It was discovered that the sonographic values of cervical length were different in both groups. The difference was statistically significant ($t = 4.82$, $p < 0.001$). Not only the length but also the number of changes on the internal cervical os was statistically significantly different ($\chi^2 = 32$, $p < 0.0001$) between both groups.

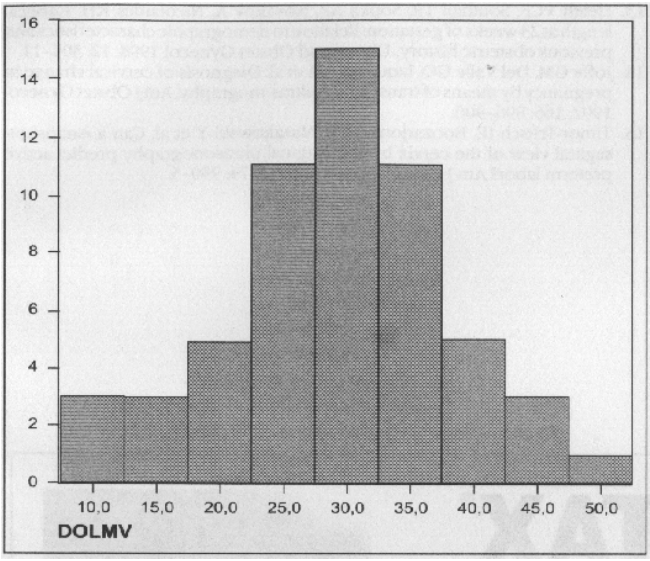


Fig. 2. Frequency distribution of cervical length (DOLMV) in mm with 5 mm interval limits for class in the group of 57 pregnant women with clinically incompetent cervix.

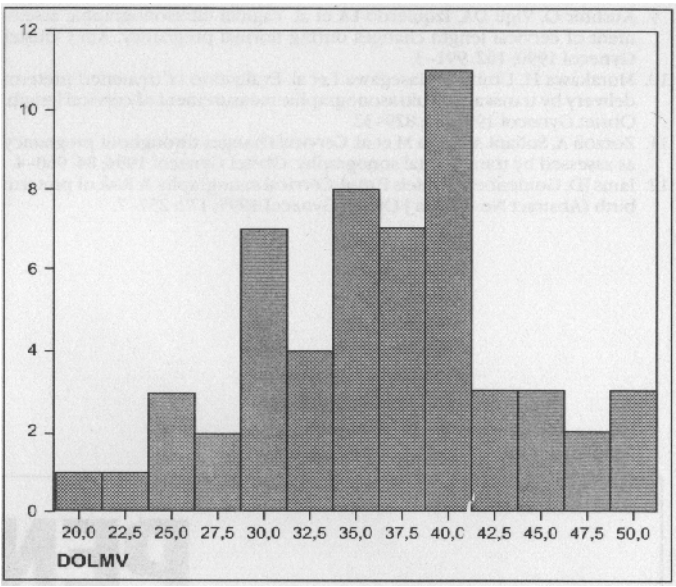


Fig. 3. Frequency distribution of cervical length (DOLMV) in mm with 2.5 mm interval limits for class in the group of 55 pregnant women with clinically competent cervix.

DISCUSSION

With regard to clinical examination, the pregnant women were divided in a clinically suspicious and an unsuspicious group. In the past however, these criteria indicated a cerclage. US allows the control and assessment of anatomical changes of the cervix in pregnancy, especially an evaluation of cervical length and of the shape of the internal cervical os.

The mean cervical length in our control group was 36.5 mm (median 37 mm), which is about 10 mm shorter than the mean cervical lengths or median values of cervix studies for pregnant women at low risk of cervical incompetence (9-13). The difference was the result of inclusion criteria, which in themselves determine the group with higher risk of premature birth.

The mean cervical length in the clinically suspicious group was shorter by an additional 7 mm and was statistically significantly different ($p < 0.001$) from the values in the control group.

Sonographic measurement of cervical length and especially the evaluation of the internal cervical os have precedence over digital examination of the cervix in diagnosing cervical incompetence (14, 15).

However, in more than half of the cases in the study group the cervical length values were unexpectedly high for an incompetent cervix. This was also reflected by the low percentage of (at least minimal) changes of the internal cervical os shape, found in 39% (22/57).

References

1. Iams JD, Johnson FF, Sonek J et al. Cervical competence as a continuum: A study of ultrasonographic cervical length and obstetric performance. Am J Obstet Gynecol 1995; 172: 1097-106.
2. Anderson ABM, Turnbull AC. Relationship between length of gestation and cervical dilatation, uterine contractility, and other factors during pregnancy. Am J Obstet Gynecol 1969; 105: 1207-14.
3. Saling E. Prämaturitäts - Dysmaturitäts - Präventionsprogramm (PDP - Programm). Z Geburtsh Perinat 1972; 176: 70-80.
4. Diener L. Die Veränderung des Zervixstatus während der Schwangerschaft. Zbl Gynäkol1979; 101: 224-8.
5. Papiernik E, Bouyer J, Collin D et al. Precocious Cervical Ripening and Preterm Labor. Obstet Gynecol 1986; 67: 238-42.
6. Bouyer J, Papiernik E, Dreyfus J et al. Maturation Signs of the Cervix and Prediction of Preterm Birth. Obstet Gynecol 1986; 68: 209-14.
7. Cunningham FG, MacDonald PC, Gant NF et al. eds. Williams Obstetrics. 20th ed. Stanford, Connecticut: Appleton & Lange, 1997: 588-90.
8. Iams JD. Cervical Incompetence. In: Creasy RK, Resnik R eds. Maternal – Fetal Medicine. 4th ed. W. B. Saunders Company, 1999: 445-64.
9. Kushnir O, Vigil DA, Izquierdo LA et al. Vaginal ultrasonographic assessment of cervical length changes during normal pregnancy. Am J Obstet Gynecol 1990; 162: 991-3.
10. Murakawa H, Utumi T, Hasegawa I et al. Evaluation of Threatened Preterm Delivery by Transvaginal Ultrasonographic Measurement of Cervical Length. Obstet Gynecol 1993; 82: 829-32.
11. Zorzoli A, Soliani A, Perra M et al. Cervical Changes Throughout Pregnancy as Assessed by Transvaginal Sonography. Obstet Gynecol 1994; 84: 960-4.
12. Iams J, Goldenberg R, Meis P et al. Cervical sonography & Risk of preterm birth. (Abstract No. 1). Am J Obstet Gynecol 1995; 172: 257.

13. Heath VCF, Southall TR, Souka AP, Novakov A, Nicolaides KH. Cervical length at 23 weeks of gestation: Relation to demographic characteristics and previous obstetric history. Ultrasound Obstet Gynecol 1998; 12: 304-11.
14. Joffe GM, Del Valle GO, Izquierdo LA et al. Diagnosis of cervical change in pregnancy by means of transvaginal ultrasonography. Am J Obstet Gynecol 1992; 166: 896-900.
15. Timor-Tritsch IE, Boozarjomehri F, Masakowski Y et al. Can a ″snapshot″ sagittal view of the cervix by transvaginal ultrasonography predict active preterm labor? Am J Obstet Gynecol 1996; 174: 990-5.

NEONATAL CARE IN MARIBOR

Silva Burja, Andreja Tekauc Golob, Bojan Korpar, Milena Treiber, Jože Žolger

ABSTRACT

Perinatology offers both pediatricians and obstetricians a very wide space for interdisciplinary teamwork. The development of such a perinatal service is an exciting advance. Its quality and level are highly related to geographical characteristics of a certain country, the yearly number of newborns in a certain region, the percentage of transports in uterus, furthermore with sufficient space conditions in a hospital, sub-specially and highly educated staff and modern equipment of the department of perinatology.

The majority of high-risk pregnancies from the northeastern part of Slovenia and all deliveries from the Maribor region are concentrated at the Department of Perinatology (University Hospital Maribor) with obstetric and neonatal service with two levels of neonatal care – normal and special care. The third level of neonatal care – the Neonatal Intensive Care Unit (NICU) is located within the Pediatric Intensive Care Unit (PICU) in the nearby building – the Department of Pediatrics. This regional neonatal referral NICU serves a number of other obstetric services (Ptuj, Murska Sobota, Slovenj Gradec) as well.

There are many reasons why we have decided on a combined model of neonatal care in two separate departments of University Hospital Maribor (yearly number of newborns, short distance between the two departments, well organized complete neonatal team on 24-hour duty at the Department of Perinatology, exactly defined procedures of primary care and stabilization of high-risk newborns and their transfer to the Department of Pediatrics NICU and finally - finances).

Many of the factors contributing to the improvement in perinatal statistics are of a socioeconomic, educational or political nature. Nevertheless, the provision of proper neonatal care for the newborn infant at risk is also very important, because the effects of care in these earliest days can be marked and long lasting.

Key words: Slovenia, perinatal service in Maribor, high-risk newborns, special neonatal care, intensive care

INTRODUCTION

Ideally, an Neonatal Special Care Unit (NSCU) and Neonatal Intensive Care Unit (NICU) should be closely integrated with an obstetrical unit, so that competent personnel are available to treat neonatal emergencies in the delivery room (1). The organization of neonatal intensive care is also varied, as the EUROPET project report makes clear (2). Moreover, levels of care are defined differently in different places. The greatest heterogeneity in definitions is observed for level II units, which cover a broad range of intermediary or special care settings.

For high-risk infants who do not require immediate resuscitation, potential problems can be identified from a systematic assessment of birth weight and gestational age (3). Additional problems will be recognized through systemic routine observation of the newborn infant. Stabilization and intervention procedures should be directed toward the prevention or treatment of the most likely complications. Approximately 30% of newborns have defined perinatal risks, transitional conditions, and mild illness such as jaundice and exclusion of sepsis. The goal is rapid diagnosis and assignment of the infant to an appropriate level of neonatal care (regular nursery, special care, intensive care) contingent on clinical findings (4, 5). More than half of this group of high-risk newborns need more or less intensive supervision of vital signs for a short or longer period (2, 3) and a relatively small per cent (3 - 5%) of all live births or between 10 - 12% from the high-risk group of newborns are treated in the NICU (1, 6, 7).

Because of the increasing complexity of perinatal care and the emphasis on early access, triage of perinatal patients has assumed growing importance. High-risk perinatal patients must be identified during the early prenatal period, intra partum and neonatal period. Participating hospitals must establish criteria for the transfer of patients within the region and develop support services, education and patient transport. The interaction between hospitals should be both bilateral and constructive.

Despite efforts to identify high risk perinatal patients during the antepartum period, as many as 30 - 50% of infants who ultimately require additional neonatal care will not be recognized until the late

intrapartum or early neonatal periods (8). The critically ill neonate must have immediate care and stabilization at the time of delivery. Supportive care needs to be maintained until either the infant is out of danger or the transport team has arrived and assumed care. Stabilization and intervention procedures should be directed towards the prevention or treatment of the most likely complications (9).

The American Academy of Pediatrics in its Guidelines for Perinatal Care (10) and the British Paediatric Association as well as the British Association for Perinatal Paediatrics (11) have issued a memorandum describing levels of neonatal care, giving criteria for assigning sick infants to intensive or special care, and detailing the staffing levels and facilities currently recommended for proper care.

MINIMUM STANDARDS OF NEONATAL CARE FOR MATERNITY UNITS AT DISTRICT GENERAL HOSPITALS (10, 11):

A regional obstetric-neonatal center with 1500 – 3000 births every year

It would accept a cross-section of obstetric deliveries including high-risk mothers. It would require:

- Skilled resuscitation at birth. A member of the pediatric staff must be on duty 24 hours a day and could be called to the labor ward to provide resuscitation.
- A special care baby unit.
- Facilities for short-term intensive care would be provided for babies who are ill for only a short time or until they can be transferred to a neonatal intensive care unit.
- In order for this to operate efficiently, the pediatric unit should be sited close to the maternity unit.

Distribution of special and intensive care cots

- Five special care cots and one intensive care cot must be provided for each 1000 deliveries per year.
- Some special care cots may be provided at the mother's bedside rather than in the special care baby unit.
- The distribution of intensive care cots should be in accordance with regional needs of perinatal care.

Medical staff – district general hospital

Any hospital with a special care baby unit must have at least two pediatric consultants on staff.

- A special care baby unit must have a resident pediatrician in the hospital round the clock.
- Designated regional neonatal care units must have two whole-time equivalents of consulting pediatricians. The hospital must have two pediatricians on duty in the building at all times. At least one of these pediatricians must be experienced in neonatal care.

Nursing and midwifery staff

Every special or intensive care baby unit must have a recognized nurse/midwife establishment of its own.

- The recommendations that there should be one nurse per special care cot and three per intensive care cot must be regarded as the minimum. At least two experienced nurses able to resuscitate babies should be on duty in each shift in a special or intensive care unit.

Medical examinations

Every newborn baby must be fully examined within 24 hours of birth by a doctor with experience in newborn care. The baby must be examined again at discharge. The results of these examinations must be recorded in the infant's records.

Medical records

Every newborn baby must be given an independent identification number at birth and a personal medical record.

Resuscitation

At all times, in all maternity units, there must be someone available in the labor ward (or within reach in two minutes) capable of starting expert neonatal resuscitation.

Equipment and laboratory services

Every special care baby unit providing continuous oxygen therapy must have a blood gas analyzer on site, the ability to X-ray an infant, and the equipment to provide at least short-term mechanical ventilation within the unit.

All special care baby units must have access to a full laboratory service; in particular, the results of urgent investigations such as blood glucose, plasma bilirubin, hemoglobin and CSF examination should be available within three hours.

Family support

The admission of a newborn baby to a special care baby unit is an emotional and stressful time for a family and makes the emotional attachment of a mother to her baby very difficult indeed. Every effort must be made to encourage good relationships within the family. Parents must be allowed to visit their babies at any time throughout the day and night.

Every special care or intensive care unit must have resident accommodation for mothers either within the unit or very close to it.

There should be at least one designated social worker for every special or intensive care unit.

It is of great importance that *minimum* standards should not be regarded as *optimum.*

Clinical categories of neonatal care

Intensive care

Should be provided for those babies:

- Receiving assisted ventilation and in the first 24 hours after its withdrawal.
- Receiving total parenteral nutrition.
- With cardiorespiratory disease which is unstable, including recurrent apnea requiring constant attention.
- Who have had major surgery.
- Who are having convulsions.
- Of less than 30 weeks gestation during the first 18 hours after birth.
- Being transported by intensive care unit staff between hospitals or for special examinations or treatment.
- Undergoing special medical procedures such as arterial catheterization, peritoneal dialysis.

Special care
Should be provided for babies:
- Requiring continuous monitoring of respiration or heart rate, or by transcutaneous transducers.
- Receiving additional oxygen.
- Being given intravenous glucose and electrolyte solutions.
- Who are being tube fed.
- Who have had minor surgery in the previous 24 hours.
- Undergoing phototherapy.
- Receiving special monitoring (for example frequent glucose or bilirubin estimations).
- Needing constant supervision (for example babies whose mothers are drug addicts).
- Being treated with antibiotics.
- With conditions requiring radiological examination or other methods of imaging.

Some units may find it useful to make a subdivision into high- and low-dependency special care to allow more detailed audit of their workload.
Special care may take place in a postnatal ward, particularly in an area specially set aside for the purpose.

Normal care
Minimal requirements are low-reading thermometers, facilities for clearing the upper airway for cord and skin care and for weighing the baby. Emergency resuscitation equipment must be readily available.

What does neonatal care look like in Maribor?
Ten years ago, and two years after the University Hospital Maribor (UHM) Department of Perinatology moved to a new building close by the Department of Pediatrics, neonatal care was reorganized completely. We have accepted to a great extent the suggestions found in the Guidelines for Perinatal and Neonatal Care (American Academy of Pediatrics) (10) and instructions of the British Paediatric Association and Perinatal Paediatrics (11).

In accordance with regulations of the International and Slovene Association for Pediatrics, Neonatology and Perinatology, the UHM Department of Perinatology, where approximately 2000 newborns are born per year, has its own NSCU. At UHM the highest profile

(level III) - intensive care of the sickest infants, involving intensive application of personnel and technology - is located at the Department of Pediatrics PICU with NICU.

There are many reasons why we have decided on a combined model of neonatal care in two separate departments (Fig. 1) (yearly number of newborns, short distance between the two departments, well organized complete neonatal team at the Department of Perinatology on 24- hour duty, exactly defined procedures of primary care and stabilization of high-risk newborns and their transfer to the Department of Pediatrics NICU and finally - financing).

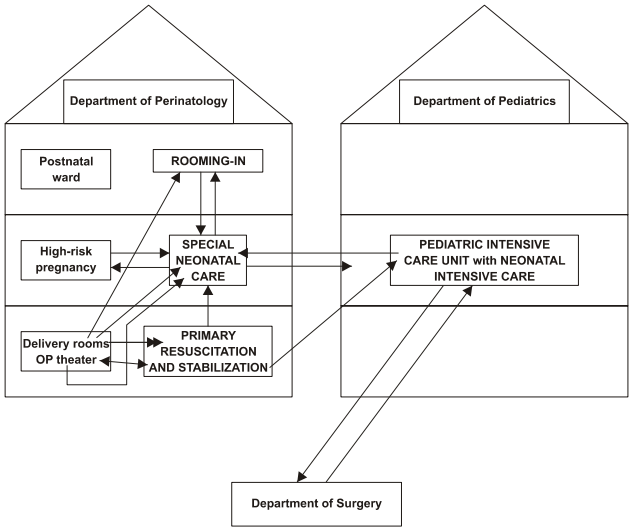


Fig.1: Neonatal care in Maribor

Neonatal functional units at the Maribor Department of Perinatology

Within our neonatal service we have facilities available to perform the following functions:

- Resuscitation and stabilization
- Admission and observation
- Normal newborn nursery care

- Rooming-in care
- Special care

The physician's and nurse's assessment of the neonate's condition determines the subsequent level of care. Most neonates are taken from the admission and observation area to the postpartum area for rooming-in.

If the baby's condition is stable, breastfeeding can be initiated in the delivery room.
Some neonates require transfer to a special care area.

After birth, **candidates for admission to the special care unit** are infants of any birth weight with any medical or surgical problems – premature babies, small for dates, infections, transitional problems, jaundice, birth injuries, congenital malformations, etc. (Fig. 2).

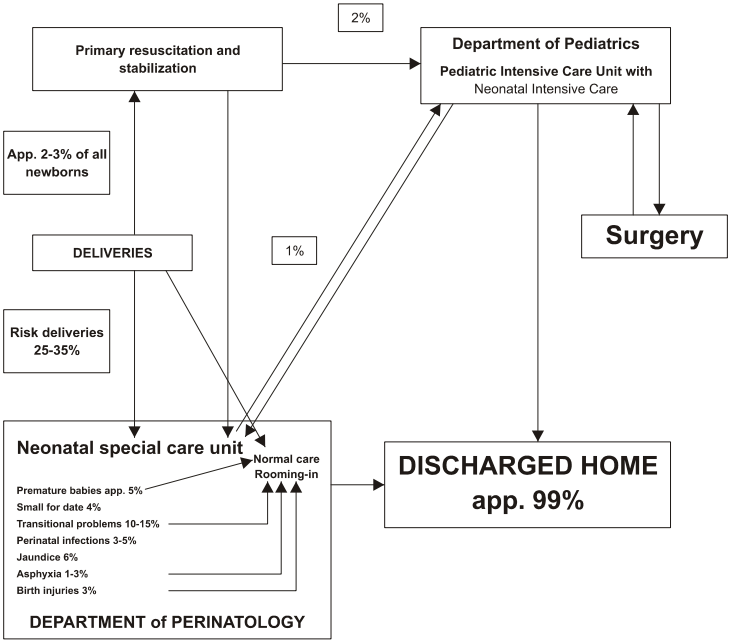


Fig.2: Neonatal care in Maribor

Resuscitation in the delivery room does not always end with the establishment of normal breathing, heart rate, and color. All babies who require more than 30 seconds of assisted ventilation or who require epinephrine, volume expanders, or chest compressions should be cared for in a special care area that can provide careful observation and vital signs monitoring to meet the continuing needs of the baby. Candidates include infants born in or out of the hospital, and those who have gone home and are returning with a problem.

Babies with complex care needs – especially **babies born at 27 weeks gestation or less are cared for initially in a level III unit.** The greater the immaturity, the more needs to be done to support the babies breathing and to protect it from infection. Thus even "well" very premature babies require intensive care simply to support their life until their organ systems undergo maturity. This includes sophisticated mechanical ventilation with oxygen, intravenous feeding, and the use of incubators to control body temperature and protect from infection. It also involves treatment of illnesses, which are more common in such vulnerable babies. The NICU is also required for a small number of larger, more mature babies who become ill from complications of delivery, from infection or metabolic disorders, or when surgical or other treatment is required for congenital anomalies.

Immediate plans for the baby should be discussed with the mother and the father before the baby leaves the delivery room. Whenever possible, they should have the opportunity to see and touch the baby before she or he is transferred to the ICU.

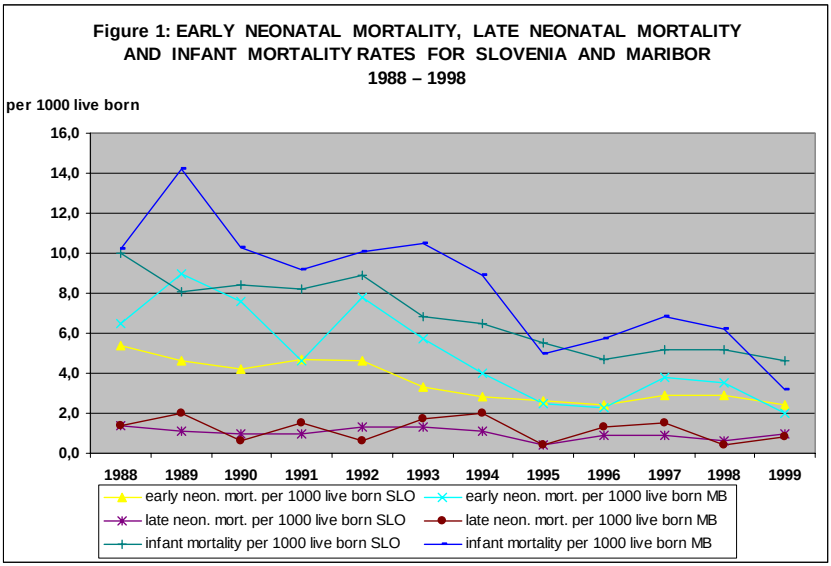


Fig. 3. Trends in neonatal and infant mortality in Maribor and Slovenia.

CONCLUSIONS

Neither the introduction nor the development of regionalized perinatal and neonatal care is an easy task. Many institutions and disciplines are involved, and conflicts of interest are bound to arise. It is a multidisciplinary task that requires a strong commitment to a common vision and close collaborative efforts by individuals, national professional bodies and government at both the central and regional levels.

References

1. Rosseger H, Stein J, Winter R, Maurer G. Modell und Ausrüstung einer Spezialpflegeeinheit fur Neugeborene (SCU) an einer Gebärklinik. Klin Paediat 1983; 19: 195.
2. Papiernik E, Zeitlin J, Milligan D et al. Variations in the organisation of obstetric and neonatal intensive care in Europe. Prenat Neonat Med 1999; 4 (suppl 1): 73-87.
3. Ballard JL. A simplified assessment of gestational age. Paediatr Res 1977; 11: 374.
4. Swyer PR. The regional organisation of special care for the neonate. Clin North Amer 1979; 17: 761.
5. Zupancic JAF, Richardson DK. Characterisation of the Triage Process in Neonatal Intensive Care. Paediatrics 1998; Vol 102, No 6: 1432-6.
6. Korones SB. Evolution of nursery design and function. Clin Perinatol 1983; 10: 127.
7. Schaefer KH. Aktuelle Fragen: Von der Deutschen Gesellschaft fur Kinderheilkunde beschlossene Richtlinien fur die Betreuung von Risikoneugeborenen. Mschr Kinderheilk 1975; 123: 41.
8. Ledger WJ. Identification of high risk mother and fetus: Does it work? Clin Perinatol 1980; 7: 125.
9. Merenstein GB, Gardner SL. Handbook of neonatal intensive care. Mosby Year Book 1993; 2: 6-20.
10. American Academy of Pediatrics. Guidelines for Perinatal Care. 4th ed. Elk Grove Village, IL: American Academy of Pediatrics, 1997.
11. British Paediatric Association. Archives of Diseases in Childhood, 1985; 60: 599-600.

BIOPSYCHOSOCIAL ASPECTS OF OBSTETRICS AND GYNECOLOGY

Zlatka Rakovec Felser

ABSTRACT

In order to understand the biopsychosocial issues in obstetrics and ginecology a basic understanding of female reproductive cycle is needed: the woman's life and her health problems are marked by several major events: by the onset of menstruation and her sexual activity, by the pregnancy and the transition to the first time parenthood, and finally, by the onset of menopause.
Each of these woman's life milestones can be connected with many of psychological, psychosexual or psychosocial problems. It can lead to her health - compromising behaviour or be one of the reasons or the consequences of her illness.
The medicalisation of women's functioning has had both positive and negative effects on women's quality of life. It has lead to a greater need for women to be informed decision-makers and have active participation in their health care. But it has also lead to greater identification and treatment of psychological conditions associated with reproduction (Boston Women's Health Book Collective, 1992).
Making overview how the health psychologist can contribute to the evaluation and treatment of obstetrics and ginecology patient the part of this article introduces some of the problems in doctor-patient communication too.

Key words: biopsychosocial model of health and illness, female reproductive cycle, psychological problems of women, doctor-patient communication, nonadherence

INTRODUCTION

From the biomedical to the biopsychosocial model of health and illness

The idea that the mind and the body together determine health and illness implies a model for studying these issues. This model is called the biopsychosocial model. As its name implies, its fundamental assumption is that any health or illness outcome is a consequence of the interplay of biological, psychological and social factors (G.L. Engel, 1977, 1980, G.E. Schwartz, 1982).

The **biomedical model**, which governed the thinking of most health practitioners for the last 300 years, maintains that all illness can be explained on the basis of aberrant somatic processes. So the biomedical model is primarily a **reductionistic model** – it reduces a person and its illness to the level of disordered cells and chemical imbalances. It is also a **single–factor model of illness** (one way cause-consequence model). It understands the illness only in terms of biological malfunctions (rather than recognizing that a variety of factors, only some of which are biological, may be responsible for the development of illness). Such a view also clearly incorporates **the mind-body dualism**, maintaining that mind and body are two separate entities. And finally, the biomedical model emphasizes **illness over health**. It is focused on aberrations that lead to illness rather than on the conditions that might promote health (G. L. Engel, 1977).

On the other hand, **the biopsychosocial model** maintains that **health and illness** are caused by multiple factors and produce multiple effects. It recognizes the importance of both – **macro level processes** (such as the existence of social support or the presence of depression) and **micro level processes** (such as cellular disorders or chemical imbalances).
Health, illness and medical care are all interrelated processes, involving interacting changes within the individual and on these various levels.
To address these issues impels researchers and clinicians toward **interdisciplinary thinking and collaboration.** As the processes of diagnosis and treatment should always consider the interacting role

of biological, psychological and social factors, the role of the interdisciplinary team increases (G.E. Schwartz, 1982).
And finally, such a holistic view of health and illness problems also makes explicit the importance of the **relationship between patient and practitioner** (1).

THE PSYCHOSOMATIC ASPECTS OF OBSTETRICS AND GYNECOLOGY

Beginning and development

Psychosomatic phenomena first attracted increased attention in gynecologic and obstetric practice during the second half of the twentieth century. A group of physicians (H. Deutsch, F. Alexander, M. Bleuler, G. Gondrau, M. Balint, L. Friedman, M. Mead, V. von Weisäcker, T. Benedek, E. Schätzing, K. Jaspers, A. Jores, W. Liepman, K. Lucas, F. Meerwein, H.M. Wolfrommm, H. Ziolko, A. Mitscherlich, etc.) dedicated to psychosomatic medicine initiated the establishment of The International Society of Psychosomatic Obstetrics and Gynecology (ISPOG, 1. Congress in Paris, 1962) (2).

The obstetrician or gynaecologist is often a woman's primary care provider and may be the first person she consults for medical and psychological problems. As Mathis, 1967 noted “Sex, reproduction and the reproductive system are almost synonymous with emotional reaction in our culture…The physician who assumes this responsibility automatically becomes involved in patient's emotional situation unequalled in any other branch of medicine.” Unfortunately, he/she is usually limited in the amount of time, may be ill-prepared to deal with the psychological needs of his/her patients and be not trained in effective patient-practitioner communication (3).

The biopsychosocial aspects of the female reproductive life cycle

The woman's life and her health problems are marked by several major events:

- The **onset of menstruation** at puberty, around the age of 11, signifies the beginning of the woman's reproductive potential.

- The **onset of sexual activity** marks a second psychological and developmental milestone.
- **Pregnancy** and the transition to first time **parenthood** is another important event, both physically and psychologically.
- **Menopause** is the final milestone in a woman's reproductive life.

The period of **the onset of menstruation and the sexual activity** is connected with the biopsychosocial problems as they are:
- **premenstrual syndrom** (PMS)**,**
- **eating disorders** (obesitas, bulimia, anorexia),
- **violence and sexual abuse,**
- **problems of self-concept and self esteem** (the physical self, the achieving self, the social self, the private self),
- **sexual or partnership problems, disorders of sexual orientation,**
- **headache, chronic pelvic pain, etc.**

Pregnancy and childbirth are significant developmental milestones for most women. Physical, intrapersonal and relationship adaptations are needed to successfully adjust to pregnancy and new motherhood.
Unfortunately, a minority of women is not able to anticipate the changes and to prepare for them accordingly:
- **transient emotional reactions** (shortly after birth, subsides without intervention in two weeks),
- **postpartum depression** (10%, two weeks after delivery and persist several months): depressed affect, loss of interest in activities, sleep difficulties, difficulty caring for the baby, guild, suicidal ideas, etc.,
- **sexual and parenthood role conflicts** and **ambiguities,**
- **quality of family and partner relationships**,
- **grief reactions to sudden loss** (pregnancy loss, stillbirth, child death),
- **infertily and its treatment** (15% of couples are infertile, only 24% of them seek medical treatment, often lead to depression).

Significant biological and psychological changes occur for women in mid-life (Hutchinson, 1993). With hormonal changes **in menopause** (estrogen deficiency), s**ignificant psychological, psychosexual and psychosocial changes and events** may also occur, such as:

- **nervousness, irritability, depression, decreased social adaptation,**
- **changes in body image, in sexual desire and functioning** (sexual responsiveness, dyspareunia, decreased sexual frequency, decreased sexual desire),
- **changes in relationship with children, loss or illness of parents, marital instability or widowhood** (3).

Health and illness, the interaction of biopsychosocial factors in woman' life:

Sometimes the psycho or psychosocial problems could contribute to the outbreak or to the progress of illness, could reduce the effects of ordered therapy or complicate the later processes of patient's rehabilitation :

- **stress-illness relationship**, dimensions of stressful events and cognitive, emotional and behavioural responses,
- **coping strategies** as mediator between perception of illness, beliefs, illness behaviour and outcome,
- **emotional responses to chronic illness**: anxiety, depression, denial defence mechanism of avoiding the implications of an illness,
- **the quality of life among the chronically ill,** the degree to which illness intrudes into someone's physical status and functioning, psychological status, social functioning and disease or treatment-related symptomatology (1).

Such psycho or psychosocial factors influence frequently the degree of patient's compliance in patient-doctor relationship – could have negative effects on trying to modify her/his poor health habits, to achieve a healthy lifestyle or to maintain the patient's health behaviour change. So, it is important that gynaecologist or obstetrician get an insight also into such themes as they are:

- the doctor-patient relationship and their communication,
- the problems of **patient's non/adherence in treatment regimen and care**,
- the medical staff, their roles, interactions and satisfaction and
- phenomena **of burn-out syndrome.**

Improving doctor patient communication and reducing nonadherence

Many factors impede effective doctor-patient communication. Doctors contribute to poor communication by not listening, by using jargon-filled explanations, by alternating between overly technical explanations and infantilising baby talk, by communicating negative affect or expectations, and by depersonalising the patient.
Patients contribute to poor communication by failing to learn and remember details of their disorders and treatment by failing to give doctors correct cues about their complaints, and by failing to follow through on treatment recommendations. Patient anxiety, lack of intelligence, lack of experience with the disorder, and incomplete information or faulty cues about the meaning of symptoms interfere with effective communication as well.
Because the physician usually receives little feedback about whether the patient followed instructions or if the treatment were successful, it is difficult to identify and correct these problems in communication.
Communication is one of the main factors leading to high rates of nonadherence. Poor communication has also been related to the initiation of malpractice litigation.
Adherence is lower when recommendations do not seem “medical”, when lifestyle modification is needed, when complex self-care regimens are required, and when patients have private and conflicting theories about the nature of their illness or treatment.
Adherence is increased when patients have decided to adhere, when they feel the doctor cares about them, when they understand what to do, and when they received clear, written instructions.
Efforts to improve communication have included training in communication skill and taking full advantage of the physician's patent professional role. Face-to-face communication with a physician can enhance adherence to treatment because of personalized relationship that exist (1).

A client-centred approach in daily practice with patients

Talking with people about their feelings requires **three basic attitudes** in the listener (Rogers, 1951):

- **empathy**, the ability to sense the other person's world of felt meanings as if they were your own, the ability to step into the other person's shoes;
- **unconditional positive regard,** a positive, warm, accepting response to the other person, regardless of how difficult his or her behaviour may be at the moment; Respect and liking for the other person, eye contact;
- **openness to feelings,** communicating to the other person that whatever the feeling is, we can reply to that and deal with it.

Listening for the feeling in what the other person is saying and reflecting that feeling back to the person in a simple, accepting manner.
Invitations for the other person to share their feelings **("door openers")** include:
- **silence;**
- **a nonverbal attending attitude:** eye contact, open body posture, communicating that you are there for the other person and want to hear what he has to say to you;
- **encouraging noises such** as "Oh, yes, I see";
- **encouraging sentences** such as "It sounds like this must be very hard for you" or "Would you like to say a bit more about that?".

The reception and reflection of feelings technique can be especially useful for the members of medical staff who have not had any training in psychotherapy in such situations as:
- assessing the **patient's needs for information**,
- during **the bad news consultation**,
- sensitivity to **sudden loss** psychological reactions,
- in identifying **stressful life events, coping style, levels of social support**,
- to formulate a psychodynamic life narrative, placing this **illness in the context of meaning of the patient's overall life trajectory**,
- to help the patient express his **feelings about the illness** (4).

Not only verbal but also nonverbal communication can create an atmosphere of warmth or coldness. A forward lean and direct eye contact, for example, can reinforce an atmosphere of supportiveness, whereas a backward lean, little eye contact, and a postural orientation away from the patient can undercut verbal

efforts at warmth by suggesting distance or discomfort (Di Matteo et al 1986).
Improving doctor-patient communication may involve not only intervening with physicians to teach them better communication skills, but also intervening with patients to teach them methods of communicating their needs and extracting the information they desire during the visit to the doctor (1).

References

1. Taylor SE. Health Psychology. New York, London, Singapore: McGraw – Hill Int. Edit, 1995.
2. Stauber M, Kästner R. Anfänge und Entwicklungen der psychosomatischen Geburtshilfe und Gynäkologie; 36; Der Gynäkologe 2003.
3. Camic P et al. Clinical Handbook of Health Psychology. Seattle, Toronto, Göttingen, Bern: Hogrefe & Huber Publishers, 1998.
4. Watson M. Cancer patient care. Psychosocial treatment Methods. Cambridge, New York, Port Chester, Melbourne, Sydney: BPS Books. Cambridge University Press, 1991.

SPONSORS

AstraZeneca UK Limited, Ljubljana

Bayer Pharma d.o.o., Ljubljana

Hoffman-La Roche Ltd, Ljubljana

Izoelektro d.o.o., Pesnica pri Mariboru

Janssen-Cilag, Johnson & Johnson S.E., Ljubljana

Lundbeck Pharma d.o.o., Maribor

PharmaSwiss d.o.o., Ljubljana

Splošna bolnišnica Maribor

Založila in izdala:	SPLOŠNA BOLNIŠNICA MARIBOR
Ureja:	Uredniški odbor
Oblikovanje, računalniški prelom in tisk:	TABULA, Tadej Kajzer s.p.
Naklada:	200 izvodov