THESIS OF ABILITATION

OBSTETRICS AND GYNECOLOGY:
FROM MOLECULAR LEVEL TO EXTENDED
LAPAROSCOPIC LYMPHADENECTOMY

VLAD IUSTIN TICA – MD PhD

SUMMARY
My whole professional activity is focused on Obstetrics and Gynecology. The first domain of interest was the infertility, with its possible causes: male and female origin, abnormal couple behavior, age, previous contraception methods, recurrent abortions, genetic abnormalities etc.

During clinical activity I observed that laparoscopic ovarian drilling is the best choice in infertile patients with polycystic ovary syndrome, resistant to ovulation induction with clomiphene citrate.

My PhD Thesis was dedicated to IVF, studying different protocols for ovarian stimulations and the occurrence of possible side effects: either non-specific, as: weight gain, asthenia, metrorrhagia, headache, pelvic pain, aberrant leucorrhea, rush etc or specific ones.

Regarding the specific side effects we found for the first time that the values of serum cortisol one month prior the IVF cycle or the first day of the ovarian stimulation may be equivalently used as controls in assessing the variation of the hormone, even if it appears that the first ones might offer a greater significance. The IVF seems to be associated with a progressive and significant increase in serum cortisol values, from the first day of GnRH-a administration, towards a maximal value after ovulation triggering and with a return to the pre-treatment level during the month after the IVF. All cortisol values remained in the normal range. Cortisol variation is not likely related to the changes in the estradiol values during the ovarian stimulation. One can reasonably speculate that cortisol increase reflects the stress experienced by IVF patients.
Furthermore, we discovered that there is a significant γ-glutamyl transpeptidase variation during ovarian stimulation with gonadotropins / gonadotropin releasing factor agonists.

Another domain of interest was the particular aspects of normal and abnormal pregnancy. We compared efficacy using two types of partograms. The first was the classical WHO partogram (group A) and the second a new type in which we estimated and reported the sub of cervical dilatation and the position of the descending head (group B). It was noted that there was a statistically significant decrease of the duration between the initiation of active phase of labor and the delivery time (dt1 + dt2 + dt3: mean A: 318.4 ± 10.4 min, B: 246.56 ± 8.28 min).

Also observed was early initiation in the acceleration stage of the active phase in the first phase of labor (A:108.73 ± 5.29 min, B: 69.96 ± 4.99 min), shorter duration of the acceleration stage of the active phase in the first phase of labor (dt2) (p<0.001, A: 136.93 ± 4.79 min, B: 91.89 ± 4.04 min) and early initiation in the second phase of labor in women who were studied with the new partogram (B). So we concluded that the new partogram is more helpful in the recognition of the initiation of the acceleration stage during the active phase of labor and in the timely use of appropriate actions in order to achieve a safer delivery.

Regarding the impact of pregnancy on gall bladder we found that pregnancy is not associated with a higher prevalence of the cholelithiasis than the non-pregnant status. The prevalence of the biliary sludge instead, is significantly increased during pregnancy. Also, the parity degree is not related to the prevalence of cholelithiasis or biliary sludge. The risk of biliary sludge increases throughout the pregnancy. Age may play a role in the process. In conclusion, pregnancy may be a risk factor for biliary sludge, but not for cholelithiasis.

During my clinical activity I was deeply involved in the discovery of high risk pregnancies and abnormal pregnancies and looked for appropriate therapies and prophylaxis.

Regarding the premature rupture of the membranes our study, which probably selected the more serious cases where fetal extraction was imposed by emergency cesarean revealed as the main etiologic factor was hypertension. In the analysed group there is a relatively high proportion of unfavorable outcome: Maternal-Fetal mortality or necessary hysterectomy, sometimes associated with bilateral ovariectomy - so with surgically induced menopause. Our analysis is in favor of DPPNI association with premature rupture of membranes and of proportional increased severe cases in relation to the size of the retroplacentar hematoma. Two other features of the results obtained are the significantly higher incidence of DPPNI at women pregnant with male and younger patients.
My experience in ovarian pregnancies strongly supported the idea that laparoscopic minimally invasive interventions—which preserve the reproductive function of the ovary—should be considered as the first choice of treatment in such pregnancies.

We reported a particular case of anencephaly relevant by its rarity—the singularity of the anencephaly with absence of any proven risk factor—and by its obstetrical consequences. Ultrasonography clarified a difficult differential diagnosis, helped in choosing the appropriate medical strategy and in avoiding unnecessary and deleterious decisions. Appropriate prenatal care and, in appropriate cases, genetic workup would decrease the risk of this serious embryologic pathology for the fertile population.

Amniocentesis remain the main prenatal diagnostic test for pregnancies with high genetic risk and we published a study about this subject, which was an illustrative step, although other techniques or other fetal tissues or cells may yet be shown to be as or more effective. Many more steps and studies will be needed to be reached the goal that most of us who provide and study prenatal screening and diagnostic long sought after: a safe, simple economical and more accurate approach to prenatal screening.

I was and I am deeply involved in discovery and therapy of medical and surgical complications during pregnancy.

The data obtained by the authors support the hypothesis that preeclampsia could have a multifactorial cause and may result from the consequences of a persistent systemic inflammatory response. Further prospective studies of larger populations are required to develop a panel of multiple predictors to cover all possible pathogenic mechanisms. By combining different detecting markers, scientists—and, then, clinicians—may offer the possibility of establishing a screening test with a high detection rate and low false-positive rate for the accurate prediction of preeclampsia.

Another very rare case presented an association of a 11cm right ovarian serous cyst, with a torsion tendency, with a singlet pregnancy, of 6-7 weeks for which it has been chosen a conservative treatment, but which, at 16-17 weeks, got complicated with the cyst torsion and required laparotomy with cystectomy. The pregnancy evolution was afterwards without incidents until the birth at term, vaginally, of a 3200g healthy girl.

We reported a case with PMCN and, with no previous protocol, our option was a cesarean-section at the onset of the labor due to the large fetus and tumor, but the patient declined the medical advice and she uneventful vaginally delivered a healthy newborn, 3.620g (without...
forceps or vacuum extractor application during expulsion). Because the patients had an uncomplicated normal delivery, despite the presence of a large PMCN (18/17/12 cm; 11.6/10.3/10.5 cm; 12/11/5.5 cm), it is reasonable to consider the risk of cyst injury during Valsalva as being low and acceptable and it can be furthermore decreased by forceps application. If IUGR was estimated, the risk is, logically, even smaller. Finally, we concluded that with no other obstetrical special conditions, even in the presence of a large PMCN and a relative large fetus, the vaginal delivery of the newborn is safely and fully recommended.

Monitoring the HIV epidemic in Romania should remain a priority, in order to develop appropriate prevention programmes and our results should help inform future strategies for both PMTCT and prevention of sexual acquisition. Identification of HIV infected women early in pregnancy and the access to testing of “hard to reach” groups will be key challenges. Despite a relatively low seroprevalence, particularly compared with Eastern Europe and Central Asia, there is no room for complacency in Romania regarding the spread of the HIV epidemic and HIV prevention efforts in Romania should continue to be a priority.

A very important challenge today is the discover soon enough a possible fetal abnormality, especially in patients who voluntary or not were exposed to sensitive drugs.

Clomiphene treatment improves fertility through ovulation induction, which can be followed by a higher frequency of a twin pregnancy – 10% [Speroff and col., 1999], compared to 0.5% in normal population. Also, as shown in the present study, administration of this drug can initiate the ”baby-making system”: after a first clomiphene-induced pregnancy, another two pregnancies appeared at a relatively short interval. Unfortunately, one of them was also a partial mole and the other was a premature miscarriage. This observations put a serious problem: it seems very probable that clomiphene not only induces ovulation, but also increases the risk of generation of a defective ovum (or several), aspect not very clearly mentioned in medical literature. The fact that the second partial mole, histologically was more severe, is very probable the result of the ”normal” evolution of a recurrent hydatidiform mole and not a consequence of the clomiphene citrate therapy.

We reported a case of sirenomelia after treatment with carbamazepine and phenobarbithal in the first 16 weeks of pregnancy, which highlighted the very interesting hypothesis of a possible causal relationship between the combined phenobarbital and carbamazepine therapy, during fetal organogenesis period, and the occurrence of sirenomelia. This is probably the consequence of the synergistic teratogenic effect of the two antiepileptics. The mechanism by which these drugs (or
their epoxides / hydroxides derivatives) alter the development of normal blood vessels, and lead to the abnormal “vitelline artery”, remains to be elucidated. Meanwhile, this report further supports the recommendation to use only one drug in pregnant epileptic women, to prevent adverse drug-drug interactions. In addition, a careful 2D/3D ultrasound screening is mandatory for all epileptic patients during the first trimester of pregnancy for early detection of possible fetal abnormalities, due to the teratogenic risk of both seizures and antiepileptic therapy.

I continuously activated in mastology domain, breast cancer being the most frequent female malignity with a still very high rate of mortality.

Thanks to its reliability, low morbidity and good healing qualities, LDF should be considered as the first line flap for radiodystrophy treatment. Whenever breast reconstruction is desired, the TRAM technique appears as a very elegant technique with good therapeutical and cosmetical effects. But if TRAM or LDF are impossible, the omental graft still remains a good and efficient operation.

We reported a rare case of abdominal wall endometrioma, accidentally found during an iterative cesarean section, 15 years after the previous procedure. Pathologic examination clarified the diagnosis. Such a condition may be, therefore, evoked before an abdominal wall tumor, even without specific symptoms and longtime after the possible causal surgery. Relevant prophylactic attitude at the end of the cesarean section may be considered.

The transvaginal ultrasonography is a reliable method for assessing the endometrium. By its qualities (non-invasiveness, reproducibility, relatively low cost) the ultrasound selects the cases where endometrial biopsy (positive diagnosis, but with higher costs and inconvenience) is required. If in case of endometrial hyperplasia there is a consensus for the necessary attitude (biopsy), for atrophy (5mm thickness in postmenopausal period) more data is needed to remove the indication for biopsy only on strict ultrasound criteria at the symptomatic patients. The ultrasound investigation allows, also, in the same examination, detecting possible associated diseases, gynecological or not.

We reported a exceptional case of two adrenal tumors with ascites and pleurisy. These tumors have occurred at a long time one after another. We did not find such an association in the medical literature. The difficulty derived from a multitude of differential diagnosis is only comparable to the one of treatment because the patient refused to perform surgery. The only possibility of a precise diagnosis and treatment remains the surgical exploration of the abdominal cavity and the removal of the tumor with consecutive pathological examination.
We reported a rare case of urachal cyst to signal the fact that, although the urachal anomalies in adult women are a rare cause of abdominal pain and may appear in a variety of clinical forms, they should be considered in the differential diagnosis of cystic formations of the area. In most cases the diagnosis can be evoked by clinical examination and imaging. However, in the case of bulky formations, as in our case, it is difficult to determine preoperative the origin of the tumor formation - it is clarified by intraoperative exploring, preceding its surgical solution.

The main domain of interest for my experimental research remain the myometrium: mechanism of contraction, receptors and intracellular signaling pathways, hormonal and nervous influence. Although there is enough information about both morphological and pharmacological characteristics of uterine autonomic nervous supply, the precise importance of the neurological component on uterine modulation, remains to be determined. The autonomic nervous fibers, distributed to the uterus, release noradrenaline (from sympathetic endings), acetylcholine (from parasympathetic fibers), but also a great number of other compounds, which, beside the two main neurotransmitters, can modulate myometrial activity. It must be mentioned the strong hormonal dependence of the local specific receptors for almost all neuromediators, either as type (or subtype), density, sensitivity or intracellular signaling pathways. Furthermore, the association of placenta and amniotic membranes during pregnancy, modify, supplementary, not only the myometrial sensitivity to local neurotransmitters, but also the regional nervous fibers either as density or mediators release.

Our in vitro study of isolated myometrium muscle suggests that Mg^{2+} ion temporarily inhibits at therapeutic concentrations spontaneous myometrial activity in a dose-dependent manner, with efficient regimens at 2-2.5 mM, and completely stops it at a Mg^{2+} concentration of 3mM. Oxytocin-induced myometrial contractions are slower reduced, in a dose-dependent and time-dependant manner (maximum effect at 20 minutes), at much higher concentrations and with non-significant differences between pregnant and non-pregnant myometrium compared to the respective control values. The consequences could rise the question of a benefit for the treatment or prevention of premature labor (questioned by the current clinical data), but not for the uterine hyperactivity induced by the active management of labor.

Nifedipine is a powerful uterorelaxant also in normo and also in hypertensive pregnancies. So it represents a good variant for the typical antihypertensive drugs used in preeclampsia / eclampsia treatment, like MgSO_4 and hydralasine. It stops efficiently the spontaneously activity in all situations. The uterorelaxant effect differs a little, being more potent in normotensive cases.
is possible that in hypertensive pregnancies there is a better intracellular biodisponibility of Ca\(^{2+}\), making the muscle cells a little less dependent of extracellular Ca\(^{2+}\). It is important also that no difference of oxytocin-induced uterine contractility between normo versus hypertensive pregnancies was observed.

Xe C is an antagonist of IP\(_3\) channel receptors and, in consequence, blocks the IP\(_3\)-induced calcium mobilization from sensitive stores. As shown in Figure 1, it seems that during AG II-induced contraction, IP\(_3\) was responsible for 34,12±11% of total calcium mobilized in cytosol. This effect is stronger on amplitude of the contractions since the frequency is decreased only with 18.75±5%. In the physiology of the automatic uterine activity IP\(_3\) has also a significant role on amplitude of the contractions (38.79±8%). But the frequency is not IP\(_3\)-sensitive calcium stores dependent, proving that IP\(_3\) is not implicated in spontaneous membranal depolarizing.

We found that it is not a great difference between the contractil effect of endothelin I in umbilical arteries in normo-versus hypertensive pregnancies. However, it seems the tissue is more sensitive to little concentrations of endothelin I in preeclamptic/eclamptic mothers. Contrary, we observed a less powerful contractil effect to high concentrations of drug. This could be explained in order of an initial, general feto-maternal vascular hypersensibility, but in the same time in order of a more efficient compensatory systems to a potent, durable, vasoactive agents.

Ry receptors are calcium channels, situated on smooth endoplasmic reticulum sensitive calcium stores, being opened by Ca\(^{2+}\), cADPR and Ry in nM concentrations. At higher concentrations (i.e. μM) Ry blocks these receptors-channels. Based on our results, we can say that, on AGII-induced myometrial contraction, Ry 10\(^{-6}\)M showed to decrease the contractility curve with 11.62±4% and the frequency of the oscillations with 9.78±7%, respectively. It is, nevertheless, important to remember that 50-60% of the smooth endoplasmic vesicles have both types of calcium channels: IP\(_3\) and Ry-sensitive channels. Only 30% of Ry-sensitive calcium stores have the Ry receptors (20% from all smooth endoplasmic stores). This means that, although Ry 10\(^{-6}\)M blocks all the Ry-sensitive channels, a large amount of calcium, stored in smooth reticulum vesicles can be mobilized through IP\(_3\)-sensitive channels. The 11.62±4% percentage reflects the role of smooth endoplasmic calcium stores, having only Ry-sensitive calcium channels (30% from all endoplasmic calcium stores). This means that the total impact of Ry-sensitive calcium stores on AGII-induced contraction is about 38.73%. 
The weak decrease of spontaneous uterine activity after BAF administration alone, it is more probable to be the result of the normal slight reduction of the autonomic contractions, after more than one hour of strips activity, than a direct effect of BAF on myometrium. This means that lysosomal calcium stores have almost no role on spontaneous membranal depolarising. We can conclude that the activation of the NAADP-dependent signaling system by E I is implicated mainly on force generation during uterine contraction.

I teach two courses for students in the last (terminal) year of the medical studies, within the curriculum framework of the Faculty of Medicine, University “Ovidius”, Constanta. These courses are: Obstetrics & Gynecology and Sexology. Teaching means presenting lectures, overseeing clinical practice or direct involvement in the acquiring of practical skills. Besides formative, permanent assessment, we also offer summative assessment – both intermediary and final. We also use simulation and phantoms in order to enhance the facility of acquiring theoretical and practical knowledge. A part of the practical skills are assimilated by the students during the mandatory (and optional) night-shifts.

Summer practice is offered to medical students, in order to take advantage of the reduced number of students during that period of the academic year and of the large variability and diversity of medical conditions expressed by our even more numerous patients during summer.

I have coordinated and continue to coordinate the training of residents in Obstetrics and Gynecology throughout their entire training curriculum (5 years). I supervise the training offered by the different instructors and I personally train residents. Trainees are offered theoretical information throughout presentations, discussions, case reports and relevant literature review. Practical skills are acquired by residents within the framework of our simulation laboratory and from the direct, supervised, clinical activity with patients.

I stimulate, support and promote research presentations and publications done by our residents. Exchange programs and participation in local, regional, national and national scientific meetings are greatly encouraged. The international participations, scholarship and scientific prizes are some of the supporting evidence of this process.

I was Invited Lecturer in 87 International and National Scientific Congresses, Conferences and Symposiums.

I was (am): Visiting Professor - Imperial College School of Medicine – London, UK (2000). Visiting Professor – University of Louisville, USA, (2004). Associate Member – Mastology Association Northern & Southern Mediterranean – Mobile University of Mastology, Montpellier,
I am Vice-President of: National Society of Obstetrics and Gynecology of Romania; Romanian Society of Gynecological Endocrinology. Romanian Society of Ultrasoundography in Obstetrics and Gynecology.
I am Partner of: New European Surgical Academy and Executive Member - European Board and College of Obstetrics and Gynaecology, beside other 9 Scientific International Societies.
As management, organizer and activity and as visibility, I am the Chair of the Department of Obstetrics and Gynecology I – University Regional Emergency Hospital, Constanţa, Romania.
I am Coordinator of several National Health Programmes (from 2002): Elaboration of a unitary and coherent system of prenatal care monitoring; Promoting the system of prenatal care monitoring; Prevention and control in cancer; Screening in cervical cancer; Prophylaxis of the Rh isoimmunization syndrome; Prophylaxis of iron-deficiency anemia in pregnant women; Support of care for pregnant and puerperal women; Management of the Woman and Child Health Regional Program; Management of the Woman and Child Health Program at the local level; Unit of Coordination for the Woman, Child and Family Health Program; Decrease of the prevalence of iron-deficiency anemia in pregnant women; Prophylaxis and treatment of menopause-related complaint; The strategy for breast feeding; Prophylaxis and treatment of infertility; National Oncology program; Decrease of Maternal mortality through the increase in the quality and efficiency of care for pregnant and puerperal women; Prophylaxis and treatment ante- and post-natal of malformations and genetic abnormalities; Mothers’ school; Monitoring and assessment of the Woman’s and Child’s health Program.

Also I am Member of Several National Health Programmes: Prophylaxis and pre and post-natal treatment of malformations and/or genetic malformations; Setting-up of a network of pre and post-natal diagnostic centers.

In the same time I am: Member (Romanian Representative) in „Union Européenne des Médecins Spécialistes” – Brussels (2007). Member EBCOG (European Board and College of Obstetrics and Gynaecology); from 2011 Executive Member. Member – International Scientific Committee – European Society of Gynecological Endoscopy (2007); Member – FIGO task force on capacity building for member societies (2009); Member (Romanian Representative) in CPME (Comité Permanent des Médecins Européens – Standing Committee of European Doctors); Member - Working Group „Centers of excellence of training” CPME. Member – MS7 (World Organization of Specialist Doctors from Latin-language-speaking countries). (2010). Member (National delegate for Romania), member – International Scientific Committee in The International Hippocratic Foundation in Cos, member of the European Council of Medical Orders (2011). - Vice-President, European Association of Hospital Doctors (AEMH) (2012). Member – Accreditation Committee for EBCOG (European Board and College of Obstetrics and Gynaecology) Training – Debrecen – Hungary; Prague – Czech Republic. Expert – International Project “Support for the Mother and Child Health Department” from the University Center of Simulation in Medical Training of the State University of Medicine and Pharmacy „Nicolae Testemiţanu” din Republic of Moldova (2014).


For the future, on research domain I intend to continue the study on the influence of salpingectomy on ovarian physiology, for determination if salpingectomy could interfere with ovarian function – by means of endocrinological, microscopic ultrasonographic and behavioral assessment.

Also I will be focused on the Incidence of occult Adenomyosis, trying to developed an original technique of CS. We will assess this technique by different criteria targeting the quality and physiology of the uterine wall. I plan to train young physicians / scientists in performing meta-analysis. Two of the interesting subjects will be: direct access in laparoscopy and influence of myomectomy on fertility and, specifically, on abortion and prematurity.
From point of view of didactic activity I intend to change the way we teach obstetrics and gynecology: 1) for the students, I intend to create an interactive environment, centered on problem (case) – solving, rather than on lectures ‘ex catedra’ and 2) for the residents, I intend to create an environment of training through simulation - where this is possible – before practicing on patients. Scientific papers could also be the result of such activity. I will take the advantage of being a member of the ESGE (European Society of Gynaecological Endoscopy). ESGE is running “The Academy” – a world renown pioneer in simulation in laparoscopy and hysteroscopy.

After my Abilitation Thesis I will start the formalities for obtaining the right to run PhD student programs. This will be an honour for me but also, a very fruitful result for the Doctoral School in Medicine from Constanta, Romania.

I will work hard for maintaining and for increasing my visibility and my involvement in National and International Scientific Committees and Boards in order to rise the level of our university research, but also of our visibility.

I will continue to be active and visible in local, regional, national and international scientifical meetings.

A new line that is in my view is breast care – as an integrated approach. The obstetrician and gynecologist is particularly well placed to integrate the different facets and conditions / pathologies of the mammary gland.