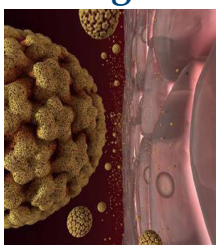
EMJ

November 2012
emjreviews.com

Gynecology & Obstetrics

Cervical Cancer Screening

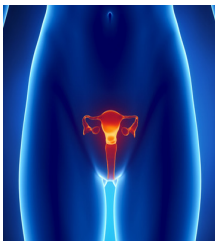
High risk Human Papillomavirus testing vs. cytology in the detection of cervical cancer



Pg 34

Early Preterm Birth

Could vaginal pH self-screening be the answer for prevention of preterm birth?



Pg 44

Ovarian Cancer

New therapeutic advances hold promise for improved outcomes in ovarian cancer patients

Pg 40

Inside: Review of the 20th FIGO World Congress of Gynecology and Obstetrics 2012, Rome, Italy.

Page 10

Arm Against Recurrent Cystitis!

«European Guidelines on Urological Infections: Grade B recommendation. Level of scientific evidence 1a»[1].

URO-VAXOM®

***E. coli* lyophilized bacterial lysate**

Prescription medication*

Preventive therapy[2]

1 oral daily for 90 consecutive days (3 months)

Prevention can be initiated at the onset or after the antibiotic treatment for the acute infection.

URO-VAXOM® is registered in more than 55 countries worldwide but not in countries such as Italy, France, Spain, UK and the Netherlands.

1. Grabe M. et al. European Association of Urology Guidelines on Urological Infections 2012. www.uroweb.org. **2.** Summary of Product Characteristics.
* Everywhere except in Serbia (OTC status).

URO-VAXOM®: C:lyophilized bacterial lysate: 6 mg. **I:** Immunotherapy. Prevention of recurrent lower urinary tract infections. Comedication in the treatment of acute urinary tract infections. **D:** treatment of acute episodes: 1 caps./day on an empty stomach for at least 10 days; preventive/consolidation therapy: 1 caps./day on an empty stomach for 3 months. **CI:** hypersensitivity to the constituents of Uro-Vaxom. **Pr:** efficacy and safety not tested in children under 4 years. Pregnancy and breast-feeding: no clinical controlled studies available. **AE:** gastrointestinal disorders (diarrhea, nausea, abdominal pain, gastric discomfort, dyspepsia), skin reactions (allergic reactions, rash, pruritus, exanthema), nervous disorders (headache) and generalized problems (slight fever). Treatment should be stopped in case of skin reactions, oedema or fever (possible allergic reactions). 30 and 90 capsules. **For further information, please contact OM Pharma SA.**

OM PHARMA SA · 22 rue du Bois-du-Lan · P.O. Box 88 · 1217 Meyrin 2 / Geneva · Switzerland
www.viforpharma.com

OM Pharma
OM PHARMA SA, A COMPANY OF THE GALENICA GROUP

Editorial Panel

Contents

EMJ

European Medical Journal - Gynecology a

editor@congressreviews.com
www.emjreviews.com

Carlton House
101 New London Road
Chelmsford
Essex
CM2 0PP

Publisher
Editorial Director
Editor
Assistant Editor
Medical Writers

Project Manager

GYNECOLOGY & OBSTETRICS

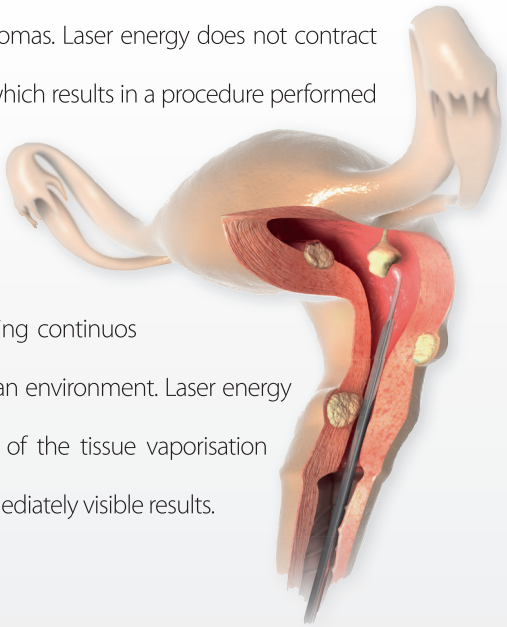
biolitec®
biomedical technology

biolitec® in Gynaecology

HOLA

*HYSTEROSCOPIC OUTPATIENT LASER APPLICATIONS

biolitec® brings you versatility of use in Gynaecology Hysteroscopic Outpatient Laser Applications (HOLA™). Using standard diagnostic hysteroscopes and specially designed fibers you can vaporise in contact polyps and myomas. Laser energy does not contract the lining muscle tissues which results in a procedure performed with minimal pain and requiring only minimal local anaesthesia.



The treatment is done using continuos flow which provides a clean environment. Laser energy allows for precise control of the tissue vaporisation with no bleeding and immediately visible results.

www.biolitec.com

biolitec biomedical technology GmbH | Otto-Schott-Str. 15 | 07745 Jena, Germany
Phone: +49 3641 519 53 - 0 / (Fax: - 33) | E-Mail: info@biolitec.de

Welcome...

I am very pleased to welcome you to the inaugural edition of ***European Medical Journal – Gynecology and Obstetrics***. This publication aims to provide influential articles from leading healthcare professionals on the latest breakthroughs in scientific research and clinical practice within women's health.

We are proud to present papers from revered gynecologists and obstetricians presenting their investigations into thought-provoking, current and global issues in the fields of gynecology and obstetrics. These issues include hypertensive pregnancy disorders, doxorubicin use in recurrent ovarian cancer, and maternal perinatal depression. The papers are reviewed and we hope will serve as useful sources of information and reference into recent advances of gynecological research.

Included in addition to the array of stimulating manuscripts, is an independent review of the 20th FIGO World Congress, held in the stunning 'Eternal City' of Rome, Italy. The Independent Federation of Gynecology and Obstetrics (FIGO) hold successful and insightful congresses every three years drawing delegates from member associations dedicated to women's healthcare from over 120 countries worldwide. This year's Congress brought together over 8,000 international healthcare professionals to present and discuss current research and results from ground-breaking investigations into surgery, medication and gynecological conditions. As expected, the Congress was hugely insightful and highlights of the innovative material presented can be found in our FIGO2012 World Congress review pages within this publication.

I hope that ***European Medical Journal – Gynecology and Obstetrics*** becomes a useful and interesting tool for healthcare professionals by continuing to provide fascinating articles and unique, in-house congress reviews.

At ***European Medical Journal***, we are pleased to receive feedback, topic suggestions or any comments that you might have, especially for this first edition. In turn, we will aim to provide an unprecedented, on-going and captivating series.

Kelly-Ann Lazarus, Editor

Help Prevent Group B Strep (GBS) Disease in *All* Babies!

According to the World Health Organization, group B strep is one of the most important causes of neonatal morbidity and mortality worldwide. You can help prevent…

…prenatal-onset GBS disease with knowledge-based strategies:

- ☑ Urine culturing for GBS followed by appropriate treatment if positive
  Thomsen AC, Morup L, Hansen KB. Antibiotic elimination of group-B streptococci in urine in prevention of preterm labour. *Lancet* 1987 Mar 14;1(8533):591–3.
- ☑ Prompt attention to vaginal infections
- ☑ Use caution regarding invasive procedures and avoid unnecessary membrane stripping

...early-onset GBS disease by implementing this proven strategy:

- ☑ Universal screening indicated treatment (you can also provide your GBS+ patients with a status card to facilitate intrapartum IV antibiotics)

…late-onset GBS disease and facilitate better outcomes by educating your patients:

- ☑ Emphasize the importance of hand washing — half of late-onset infections are from sources other than the mother!
- ☑ Emphasize the importance of breastfeeding to supply their baby with important antibodies to fight infection
- ☑ Provide materials so your patients can recognize the symptoms of GBS infection in their baby for earlier intervention/better outcomes

GROUP B STREP INTERNATIONAL

For resources and materials on how to help prevent GBS disease in babies during pregnancy through early infancy, please visit www.groupbstrepinternational.org.

FOREWORD

It is a great privilege that I have been asked, as the Chief Executive of the International Federation of Gynecology and Obstetrics (FIGO) - the only global body representing national societies of gynecologists and obstetricians - to introduce the first edition of the ***European Medical Journal - Gynecology and Obstetrics***. The support for our XX World Congress, fittingly just held in one of the great European cities, Rome, this October, perfectly illustrates the appetite for ongoing professional information and interaction. Over 8,000 participants from 170 countries experienced a rich and dynamic Scientific Programme, covering the major subspecialties of Maternal and Foetal Medicine, Reproductive Medicine, Gynecological Oncology, Urogynecology and Sexual and Reproductive Health, including women's health issues in low- and middle-resource countries.

One of FIGO's main commitments is to upgrade continually the practice of gynecology and obstetrics through research, education and training, and to maintain the highest levels of professionalism and scientific and ethical standards. FIGO recognises that gynecologists and obstetricians benefit hugely from regular reviewing of relevant professional news and articles, of which the ***EMJ*** is now a new and notable example.

It is essential that clinicians remain abreast of key advances and opinion in Europe, and I have no doubt that the ***EMJ*** will succeed in providing professionals with the most salient and up-to-the-minute developments. Busy clinicians require succinct briefing, and I am sure that this Journal will quickly develop into a 'must-read' publication among its audience.

A lively mix of review articles, case reports, practice guides, theoretical discussions and original research will ensure that readers are kept informed, and will also stimulate healthy discussion between specialties - the mark of a quality publication.

I have no doubt that the members of FIGO's European societies will consider the ***EMJ*** a welcome and invaluable accompaniment to their professional schedules, and I very much look forward to following its development.

My very best wishes,

Professor Hamid Rushwan, FIGO Chief Executive

Professor Hamid Rushwan is currently the Chief Executive of the International Federation of Gynecology and Obstetrics (FIGO). Previously, he was Professor of Obstetrics and Gynecology at the University of Khartoum, Sudan, and a former advisor to the World Health Organisation (WHO) and the United Nations Population Fund (UNFPA). Professor Rushwan has made significant contributions to the development of policies and the establishment of a number of service and research institutions in low- and middle-resource countries for the promotion of women's health.

FIGO2012 WORLD CONGRESS

FIERA DI ROMA, ROME, ITALY

7TH - 12TH OCTOBER 2012

Welcome to the *European Medical Journal* review of Gynecology and Obstetrics

The International Federation of Gynecology and Obstetrics (FIGO) is a unique global organisation which brings together leading gynecological and obstetric societies from over 120 countries around the world. Held in high regard throughout the world for its commitment to women's health, not only by its flourishing member societies, but by numerous international partners and collaborators, FIGO participates in the Alliance for Women's Health with major healthcare corporations including the World Health Organisation (WHO), the United Nations Population Fund (UNFPA) and the International Confederation of Midwives (ICM).

The triennial FIGO World Congress brings forth the meeting of delegates from each member association together with thousands of leading gynecologists and obstetricians to discuss and analyse ground-breaking gynecology and obstetrics research. Major healthcare organisations also attend presenting new medication and resources via satellite symposia throughout the meeting place.

The site for the World Congress rotates between the Africa-Eastern Mediterranean, Asia-Oceania, Europe, Latin America and North America regions of FIGO. This year, FIGO held its 20th World Congress of Gynecology and Obstetrics between 7th and 12th October in the 'Eternal City' of Rome, Italy.

The Italian capital, regarded as one of the birthplaces of western civilisation, is a vibrant city steeped in culture. World-renowned for its art and architecture including its historic centre which is listed as a World Heritage Site, Rome holds some of the worlds most visited sites such as the Vatican and the Colosseum.

The 'Eternal City', so called by the Ancient Romans, is also a major worldwide intellectual and educational centre, home to many major academies, universities and of course medical institutions. Medicine forms an important part of Ancient Roman heritage and

v of the 20th FIGO World Congress

it is apt that the FIGO2012 World Congress is hosted by a nation whose ancestors believed strongly in the prevention of disease as well as cure.

Thousands of visitors from all over the globe attended the informative scientific programme held in the Fiera di Roma congress venue which included keynote lectures, symposia and free communication sessions addressing current issues affecting women's healthcare worldwide. Pre-congress courses were also held in various hospitals throughout Rome, bringing together the Roman scientific community and international delegates wishing to improve their knowledge and skills whilst in attendance of the Congress. The issues at the forefront of the Congress included: infertility, hormonal contraceptives, ovarian and cervical cancer, post-natal surgery and aftercare, pre-eclampsia, abortion, preterm birth and adolescent gynecology.

The health-related Millennium Development Goals, as set out by the United Nations, were of particular focus at the Congress as the deadline year of 2015 is fast approaching and although significant progress has been made with regards to Goals 4 and 5, maternal and newborn mortality remain pertinent issues. Particular importance was laid upon prevention and treatment of post-partum haemorrhage and obstetric fistula, which are treatable conditions but remain a fatal cause of many maternal deaths in low-resource settings.

The importance of collaboration between global health organisations, UN agencies and the public/private sector was regularly prescribed in order to better achieve the MDGs, especially within poor and under-served populations, by implementing sustainable programmes and improving medical care available to women and newborns.

FIGO 2012 WORLD REPORT: IMPROVING WOMEN'S HEALTH

International Federation of Gynecology and Obstetrics (FIGO) target reduction in maternal mortality ratio and aim for universal access to reproductive health by 2015.

Rome, October 8th, 2012 – "Although Millennium Development Goal (MDG) 5 encompasses the reduction of maternal mortality and the improvement of sexual and reproductive health, every MDG has an impact on women's health as they affect women most: eradication of poverty, gender equality, education, reduction of child mortality, HIV/AIDS, tuberculosis, and malaria," commented Professor Sir Sabaratnam Arulkumaran, President-Elect of the International Federation of Gynecology and Obstetrics (FIGO), presenting the World Report on Women's Health at the FIGO2012 World Congress of Gynecology and Obstetrics in Rome, Italy (7-12 October 2012).

287,000 maternal deaths occurred in 2010 globally, a decline of 47% from levels in 1990.

The United Nations MDG5 - "Improve maternal health" - sets two targets: reducing the maternal mortality ratio (MMR) by 75% between 1990 and 2015, and achieving universal access to reproductive health by 2015. Although results have shown a reduction in maternal mortality, the rates in many countries to date are not what had been hoped for. According to the "Trends in Maternal Mortality: 1990 to 2010" report, recently released by the World Health Organization (WHO), the United Nations Children's Fund (UNICEF), the United Nations Population Fund (UNFPA), and The World Bank, an estimated 287,000 maternal deaths occurred in 2010 globally, a decline of 47% from levels in 1990. Sub-Saharan Africa (56%) and Southern Asia (29%) accounted for 85% of the global burden (245,000 deaths). At the country level, two countries account for a third of global maternal deaths: India at 19% (56,000) and Nigeria at 14% (40,000). The global MMR in 2010 was 210 maternal deaths per 100,000 live births, down from 400 maternal deaths per 100,000 live births in 1990. The MMR in developing regions (240) was 15 times higher than in developed regions (16).

"The medical activities that need to be implemented to prevent maternal mortality and morbidity are known, but global progress cannot be achieved unless effective policies are introduced by governments that enable women to access such care," Professor Arulkumaran explained. "The FIGO 2012 World Report on the topic of improving women's health provides ample information to allow everyone to take action at an individual, institutional, and professional level. It is a call for action based on evidence. It addresses how we can act, in addition to what has happened or what is currently going on. One single organisation or government cannot achieve these tasks. In addition to the global cooperation of partner organisations, every one of us has to take some responsibility to improve women's health," he concluded.

> *"One single organisation or government cannot achieve these tasks. Every one of us has to take some responsability to improve women's health."*
>
> *Professor Sir Arulkumaran*

The World Report - published by FIGO every three years to coincide with its World Congress - is an overview of the major areas within women's global maternal and reproductive health. "The goal of the 2012 Report – the theme of which is 'Improving Women's Health' - is to focus on these wider issues, expanding the focus for us, as professionals, beyond the traditional basic obstetric functions," Professor Arulkumaran said.

THE MILLENNIUM DEVELOPMENT GOALS (MDGS)

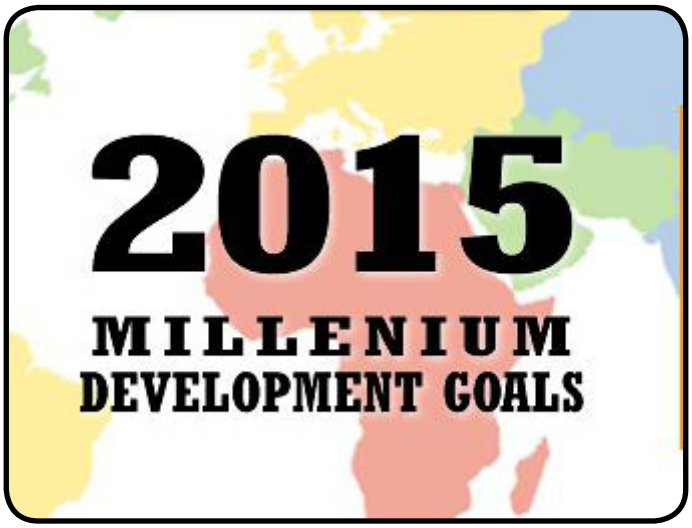
At the Millennium Summit in September 2000 the largest gathering of world leaders in history adopted the UN Millennium Declaration, committing their nations to a new global partnership to reduce extreme poverty and setting out a series of time-bound targets, with a deadline of 2015, that have become known as the Millennium Development Goals.

The Millennium Development Goals (MDGs) are the world's time-bound and quantified targets for addressing extreme poverty in its many dimensions - income poverty, hunger, disease, lack of adequate shelter, and exclusion - while promoting gender equality, education, and environmental sustainability. They are also basic human rights - the rights of each person on the planet to health, education, shelter, and security.

The world has made significant progress in achieving many of the Goals. Between 1990 and 2002 average overall incomes increased by approximately 21%. The number of people in extreme poverty declined by an estimated 130 million. Child mortality rates fell from 103 deaths per 1,000 live births a year to 88. Life expectancy rose from 63 years to nearly 65 years. An additional 8% of the developing world's people received access to water. And an additional 15% acquired access to improved sanitation services.

But progress has been far from uniform across the world - or across the Goals. There are huge disparities across and within countries. Within countries, poverty is greatest in rural areas, though urban poverty is also extensive, growing, and underreported by traditional indicators.

Sub-Saharan Africa is the epicenter of the crisis, with continuing food insecurity, a rise of extreme poverty, stunningly high child and maternal mortality, and large numbers of people living in slums, and a widespread shortfall for most of the MDGs. Asia is the region with the fastest progress, but even there hundreds of millions of people remain in extreme poverty, and even fast-growing countries fail to achieve some of the non-income Goals. Other regions have mixed records, notably Latin America, the transition economies, and the Middle East and North Africa, often with slow or no progress on some of the Goals and persistent inequalities undermining progress on others.



FIGO JOINING FORCES TO ACHIEVE HEALTH-RELATED MDGS

FIGO strengthens collaboration with UN organisations, World Federations, Non-Governmental and Faith-Based Organisations, and the Private Sector

Professor Gamal Serour, the President of FIGO whom inaugerated the opening press conference of the 2012 Congress, hopes to "continue and enhance the open dialogue between FIGO and various concerned professional organisations, United Nations organisations and global NGOs on how we can all contribute to accelerating the progress on achieving the health-related Millenium Development Goals".

> *"It is our responsability, as physicians, to provide quality care across the life-cycle, and it is our responsability, as leaders of global organisations, to join forces."*
>
> *Professor Gamal Serour*

In fact, the vision and mission of FIGO reflects the vital role health professional organisations have in the promotion of women's health and in the joint efforts to achieve specifically - but not only, as most of the MDGs have an impact on women's health – MDG-4 "Reduce child mortality" and MDG-5 "Improve maternal

influencing policy decision-making to raising awareness of issues and their solutions, to setting standards, to educating and training healthcare professionals and providers" Professor Serour added.

Child deaths are falling, but much more needs to be done in order to reach the development goal: to reduce by two-thirds, between 1990 and 2015, the under five years old mortality rate, from 93% of every 1000 dying to 31% of every 1000. Since 1990, in the developing regions, the mortality rate of under five years old has declined by 35%, from 97 deaths per 1000 births to 63. But, children in the developing regions as a whole, are twice as likely to die before their fifth birthday as children in the richest of households.

Maternal mortality has nearly halved since 1990: an estimated 287,000 maternal deaths occurred in 2010 worldwide, a decline of 47% from 1990. However, levels are far removed from the 2015 target. The targets for improving maternal health include reducing by three-fourths the maternal mortality ratio and achieving universal access to reproductive health. The regions with the highest maternal mortality, sub-Saharan Africa and Southern Asia, are also those with the lowest coverage of births attended by skilled health personnel – less than half.

Maternal health coverage has progressively increased in developing regions from 63% in 1990 to 71% in 2000, and then to 80% in 2010. Poverty and lack of education perpetuate high adolescent birth rates, and inadequate funding for family planning is a major failure in fulfilling commitments to improving women's reproductive health.

Professor Serour proposed collaboration as a clear way forward. "The three year period 2009-2012 witnessed an unprecedented strengthening of FIGO's partnerships with governmental, non-governmental, and faith-based organisations, and the private sector, and through collaborative efforts FIGO has played the role it is supposed to fulfil to the best. The health-related MDGs 4 and 5, and the others impacting women – '1- eradication of poverty', '2- achieve education', '3- gender equality', and '6-combatting HIV/AIDS, tuberculosis and malaria' – cannot be achieved without a greater effort. It is our professional responsibility, as physicians, to provide quality care across the life-cycle, and it is our responsibility, as leaders of global organisations, to join forces. Rest assured that women will no longer be the silent victims and unheard voices of substandard healthcare."

> *"Rest assured that women will no longer be the silent victims and unheard voices of substandard healthcare"*
>
> *Professor Gamal Serour*

Since 1990, in the developing regions, the mortality rate of under five years old has declined by 35%, from 97 deaths per 1000 births to 63.

FIGO PARTNERSHIPS

UNAIDS

The Joint United Nations Programme on HIV/AIDS, UNAIDS is a long-term partner of FIGO. It is an innovative partnership that leads and inspires the world in achieving universal access to HIV prevention, treatment, care and support. "UNAIDS sees professional organisations, FIGO in particular, as crucial partners in responding to the AIDS epidemic. FIGO has the credibility to ensure that basic human rights are an integral part of health services and in securing the future of women and children's health," said Paul De Lay, Deputy Executive Director of UNAIDS. "Thanks to their professionalism and integrity, professional associations can act as a voice for the voiceless" he added.

United Nations Population Fund

"FIGO is our natural partner for sexual and reproductive health and reproductive rights. We are together pushing hard to achieve the MDG-5 on improving maternal health and ensuring universal access to reproductive health. We appreciate the dedication of thousands of obstetricians and gynecologists that are on the ground, sometimes under difficult circumstances, ensuring that women survive pregnancy and childbirth and their human rights are protected," said Dr Babatunde Osotimehin, Executive Director of UNFPA – United Nations Population Fund.

World Health Organisation

"The professional associations of gynecologists and obstetricians have a critical role to play in the 24 hours around delivery, when we see most of the deaths of mothers and newborns. Particularly if there are complications, not only do they provide the clinical care directly, but also they provide knowledge and supervision to other health workers. In addition, they contribute to development of treatment guidelines and policy based on scientific evidence. In the quest for achieving MDG-4 and MDG-5, FIGO is a vital partner for us at WHO", said Dr Flavia Bustreo, Assistant Director- General Family, Women's and Children's Health, World Health Organisation.

International Confederation of Widwives

"FIGO and ICM, the International Confederation of Midwives have a long history of collaborating on improvements of maternal and newborn health. Together we play a crucial role in advocating for and providing care to the world's child bearing women. We are committed to enhance and expand our collaboration in the future towards achieving MDGs and beyond" said Frances Day-Stirk, President of the International Confederation of Midwives.

THE FIGO LOGIC INITIATIVE:

WORKING TOWARDS BETTER MATERNAL AND NEWBORN HEALTH

The FIGO LOGIC (Leadership in Obstetrics and Gynecology for Impact and Change) Initiative, funded by the Bill & Melinda Gates Foundation, is a programme created by FIGO to improve maternal and newborn health policy and practice in eight countries in Africa and South Asia, through the capacity improvement of national professional organisations of gynecology and obstetrics. The countries involved are: Burkina Faso, Cameroon, Ethiopia, India, Mozambique, Nepal, Nigeria, and Uganda.

Speaking at the FIGO 2012 Congress, Professor Hamid Rushwan, Chief Executive of FIGO admitted that despite combined efforts and recent progress, the targets set by the United Nations to acheive MDGs 4 and 5 are far from being acheived. Professor David Taylor, the LOGIC Project Director explained "The vast majority of maternal deaths are preventable, yet many thousands of women - especially in sub-Saharan Africa and Southern Asia - are dying daily as a result of complications in pregnancy and childbirth. The survival chances and health of a newborn baby are closely linked to the health and well-being of its mother. Quality newborn care starts before birth, during pregnancy, and a safe delivery with high quality postnatal care is essential for a newborn baby's chance of survival".

The FIGO LOGIC Initiative was launched in 2009 at the XIX FIGO World Congress in South Africa with the objective of strengthening the role of professional organisations in influencing maternal and newborn health policy and improving clinical practice.

"Since the beginning, we have provided support to the national organisations involved to improve their organisational capacity through dedicated training on every aspect of their work, including governance, leadership, administration of human resources, financial management, advocacy and policy change, and the improvement of clinical practice by the implementation of clinical guidelines and protocols and the development of maternal death reviews," Professor Taylor added.

The successes achieved by the FIGO LOGIC Initiative so far include:

- All associations have regular and scheduled opportunities to engage with their Ministries of Health and other partners about maternal and newborn health priorities and plans and are perceived as relevant and influential partners.
- All have contributed to the revision and/or development of clinical guidelines and protocols aimed at improving maternal and newborn survivial and health.
- All associations have developed, with their partners, multi-disciplinary facility-based maternal death reviews which learn lessons from the tragedy of a maternal death, so that care can be improved for the benefit of future mothers.

‘WHY DID MRS X DIE, RETOLD’ RELEASED AT FIGO2012

An educational video regarding maternal health has been released at the 2012 World Congress.

The video was released by the Hands On for Mothers and Babies organisation, a registered charity striving for the advancement of health and education for the benefit of pregnant women, new mothers and their babies. The charity is supported by FIGO and inspired by the work of previous FIGO President Professor Mahmoud Fathalla, who is the founder of the Safe Motherhood Initiative.

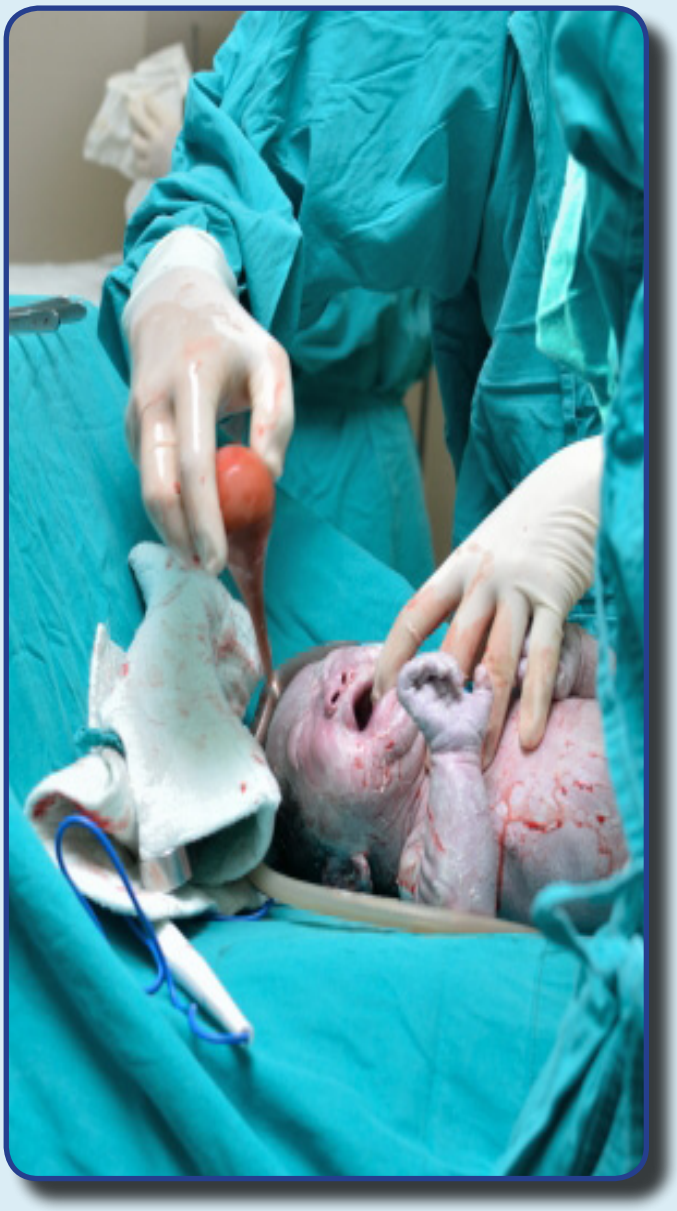
‘Why Did Mrs X Die, Retold’ is an animated journey through pregnancy to childbirth which encounters prevalent maternal dangers along the way. It is a remake of the 1980’s film ‘Why Did Mrs Die?’ produced by Professor Fathalla and the World Health Organisation.

To see ‘**Why Did Mrs X Die, Retold**’ go to:
http://www.handsonformothersandbabies.org/

“Through site missions and coaching by international experts, we have enhanced their profiles and performance: as a result, two of them, the Association of Obstetricians and Gynaecologists of Uganda (AOGU) and the Societé de Gynécologues et Obstétriciens du Burkina (SOGOB), have been approached by their respective Ministries of Health to lead national programmes of maternal death reviews.”

The completion of the project is set for October 2013, but some other important results are already tangible. For instance, with the collaboration and support of partners such as Save the Children, the United Nations Population Fund (UNFPA), and the White Ribbon Alliance, AOGU helped to influence the Ugandan government to increase funding for reproductive health by 30%.

“One of the objectives of the programme is to promote collaboration between the participating professional organisations to facilitate exchange of knowledge and best practice. We hope and expect further positive achievements to extend the impact of the LOGIC Initiative beyond the current borders,” Professor Taylor ended.



FIGO COMMITTED TO REDUCING MATERNAL MORTALITY AND COMPLICATIONS

FIGO Initiatives for prevention and treatment of post-partum haemorrhage and obstetric fistula in low-resource countries

POST PARTUM HAEMORRHAGE

Post-partum haemorrhage (PPH) is the most significant direct cause of maternal mortality in low-resource countries, accounting for approximately 30% of maternal deaths, and is one of the most preventable. The most common cause of PPH is uterine atony, a failure of the uterus to contract adequately after the delivery of a newborn.

For PPH prevention and treatment, uterotonic therapy is key and the most widely recommended agent is oxytocin. But oxytocin requires parenteral administration, as well as sterile equipment, and refridgeration, all factors hindering its use in low-resource settings.

When injectable uterotonics are neither available nor feasible, misoprostol, a synthetic E1 prostaglandin analogue, has increasingly been adopted as an alternative strategy for PPH care – one endorsed by FIGO and other international bodies. Misoprostol is available in tablet form, stable at room temperature, well absorbed orally and sublingually, and requires few skills to administer.

"Our PPH Initiative, funded by a grant to Gynuity Health Projects from the Bill & Melinda Gates Foundation, advocates for and disseminates evidence-based information on misoprostol for PPH, aimed at healthcare providers and clinical policymakers. It is part of a global project for translating scientific and operational research into effective policies, programmes and practice," Professor Hamid Rushwan, FIGO Chief Executive, explained.

OBSTETRIC FISTULA

"Another major concern for women who give birth in low-resource countries is obstetric fistula, perhaps the most tragic of preventable childbirth complications, as affected women in nearly all cases lose their babies, suffer from health problems, including chronic incontinence, are often abandoned by their husbands, forced to live in shame and social segregation," Professor Rushwan continued.

Obstetric fistula is a hole in the birth canal usually caused by prolonged obstructed labour. It is preventable and largely avoidable by delaying the age of first pregnancy, stopping harmful traditional practices, and granting timely access to obstetric care. According to the World Health Organisation, each year between 50,000 and 100,000 women develop obstetric fistula. More than 2,000,000 women live with untreated obstetric fistula in sub-Saharan Africa and Asia, where too few physicians are equipped with the skills needed to repair fistulae and care for patients following surgery.

FIGO, in collaboration with a number of stakeholders, recently launched its Fistula Initiative which focuses on the prevention and treatment of obstetric fistula in 12 African and Asian countries. "The aim of the Initiative is to ensure high quality clinical training for the care of women with obstetric fistula and to increase capacity of services and staff to provide comprehensive management and treatment of fistula through a programme of training of trainers and support to the training centres," Professor Rushwan added.

For this purpose, FIGO co-ordinated the production of a dedicated manual, the Global Competency-Based Fistula Surgery Training Manual, to enable physicians to acquire the skills needed to prevent it and provide proper surgical,

ALERE PRESENT NEW PRE-ECLAMPSIA RESEARCH

Groundbreaking study shows that a simple, rapid PIGF test can accurately risk stratify pregnant women with suspected pre-eclampsia

Alere presented new results at FIGO2012 demonstrating that a simple blood test measuring placental growth factor (PIGF) can help to quantify risk in women when pre-eclampsia is first suspected. The level of PIGF in blood is already known to be an important marker for placental and foetal wellbeing as well as the placenta's ability to sustain pregnancy.

This UK-based multi-centre study known as PELICAN used the Alere Triage PLGF test to measure PIGF levels in 625 women with suspected pre-eclampsia in their first clinic visit. In women presenting before 35 weeks gestation who were managed in accordance with standard clinical protocols, a high PIGF level was strongly correlated with low risk for required delivery in the next 14 days. In fact, 96% of women with a normal test result were correctly diagnosed as not at risk. Conversely, a low PIGF level accurately identified women at high risk for preterm delivery, and 94% of women with an abnormal test result went on to require early delivery.

Professor of Obstetric Medicine at the University of Oxford and PELICAN investigator, Christopher Redman commented, "Pre-eclampsia is notoriously unpredictable. Reliable tests that can be used in the clinical setting, when pre-eclampsia is first suspected, would be a notable breakthrough in the management of this life-threatening condition. The PELICAN data have demonstrated that PIGF testing before 35 weeks enables physicians to categorise women into low and high risk for disease progression and to adjust clinical management appropriately."

l and psychosocial care to women who
curred fistulae.

nual was produced with funding
he United Nations Population Fund
A), and with the collaboration of fistula
ns and professional and specialist health
sations. It was pilot tested in several
and is now being utilised for training in
ted centres.

s also involved in the provision of
g workshops on PPH, Minimally Invasive
y (MIS), obstetric ultrasonography, basic
l skills and pelvic floor dysfunction
y – these are conducted in many African
ian countries as the issues are highly
t to maternal mortality and morbidity.

Pre-eclampsia is a dangerous condition that can develop during pregnancy and, if left untreated, may lead to significant maternal organ damage, foetal growth restriction and, in some cases, foetal or maternal death. Deterioration in women with suspected pre-eclampsia can be rapid and unpredictable, requiring costly and frequent clinical assessment to determine if early delivery is medically necessary. Current diagnostic methods for assessing risk include measurement of maternal blood pressure, identifying the presence of protein in the urine, and laboratory blood testing for maternal organ damage. These methods are generally poor in determining a woman's level of risk and often result in over-management and unnecessary costs.

Remarking on the PELICAN results, Andrew Shennan, Professor of Obstetrics at King's College London and study investigator, stated, "The appropriate management of women with suspected pre-eclampsia presenting before 35 weeks is known to be extremely complex. Many women are admitted, treated or even delivered inappropriately. What is more worrying is that a substantial number of cases are missed altogether. At last, with the Alere Triage PLGF Test, we have a simple and reliable tool guiding clinicians to target women who will benefit from these interventions, whilst limiting unnecessary healthcare expenditures incurred by managing women at low risk for needing preterm delivery."

FIGO FACILITATE THE ACHIEVEMENT OF UNIVERSAL ACCESS TO REPRODUCTIVE HEALTH

THE FIGO FERTILITY TOOL BOX™

The FIGO Fertility Tool Box™ is a new instrument, focused on alleviating the burden of infertility, developed by the FIGO Committee for Reproductive Medicine, chaired by Professor David Adamson. "When thinking about it, we decided to focus not on sophisticated infertility treatments, such as in vitro fertilisation or other assisted reproductive technologies, but to work within the range of generalist obstetricians and gynecologists and down to lower level healthcare providers, including midwifes and the public," he said.

The Tool Box™ is simple, usable, and evidence-linked; a very flexible tool for adaptation in different environments and countries. It consists of 6 components dealing with overcoming personal and social barriers to infertility care, prevention, diagnosis, treatment, referral and resolution, plus the FIGO Fertility Daisy™.

"Infertility, specifically in low resource settings, is important and its management is justified by the positive impact on quality of life, burden of disease, political commitments, non-discrimination, family planning, prevention of sexually-transmitted infections, affordability and protection of resources - each item symbolised by a petal of the daisy," Professor Adamson said.

"It is hoped that this tool will be used by many providers of women's healthcare to increase access to quality, cost-effective infertility prevention and management. We have taken into account the international sensitivities with respect to culture, religion, politics and economics," Professor Adamson continued.

'The FIGO Fertility Tool Box™' and third release of 'Emergency Contraceptive Pills: Medical and Service Delivery Guidelines' presented at FIGO2012

Helping infertile women become pregnant and helping fertile women avoid unintended pregnancies are two sides of the same coin: reproductive health. As defined by the World Health Organisation (WHO): "Reproductive health implies that people are able to have a responsible, satisfying and safe sex life and that they have the capability to reproduce and the freedom to decide if, when and how often to do so".

The reproductive health issues of infertility and contraception formed the basis of two major FIGO presentations at the FIGO2012 World Congress in which details of 'The FIGO Fertility Tool Box™' and a new release, reviewed by FIGO, of the 'Emergency Contraceptive Pills: Medical and Service Delivery Guidelines' were announced.

Other maternal and newborn health issues continue to be tackled by FIGO's Saving Mothers and Newborns Initiative, which involves a number of leading medical organisations in its aim to achieve Millenium Development Goal 5 - "improvement of maternal health". The Initiative aims to significantly reduce maternal and newborn mortality and morbidity in 10 low and middle-resource countries, by focusing upon issues such as unsafe abortion.

Quick Guide to The FIGO Fertility Tool Box™

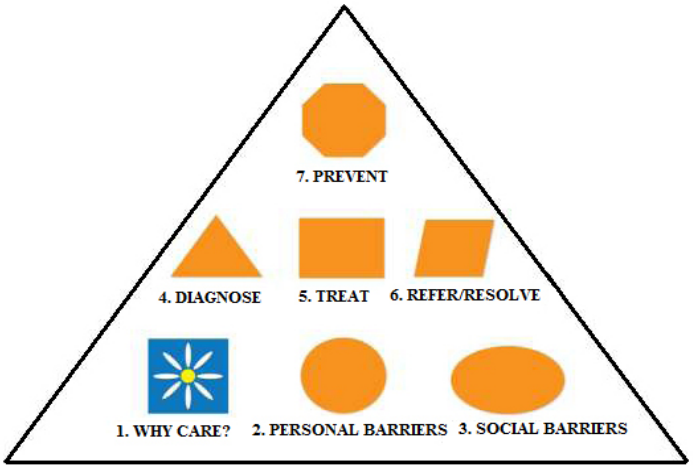
Who should use it?

Anybody who wants to help infertile people! It was designed in the first instance for health care workers, but others who want to make a difference in the lives of infertile people may also find it useful. The Tool Box is available in hard copy but also an electronic version for computers and cell phones.

What's in the Tool Box?

Seven Tools to help you tackle the disease/disability of infertility. Each Tool provides information on how to manage a particular aspect of infertility:
Tool 1: The FIGO Fertility Daisy– why we should care about infertility;
Tool 2: Overcome personal barriers;
Tool 3: Overcome societal barriers;
Tool 4: Diagnose infertility;
Tool 5: Treat infertility;
Tool 6: Refer/Resolve infertility;
Tool 7: Prevent infertility.

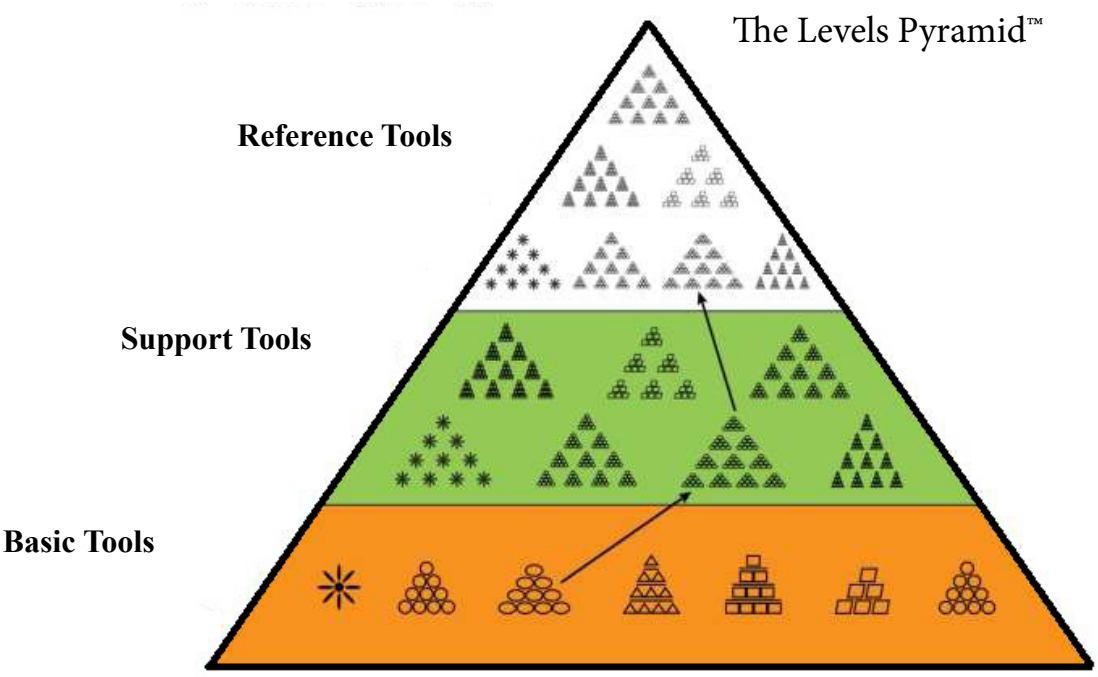
The Tools Pyramid™



How do the Tools work?

There are 3 levels of Tools.
The Basic Tools™ contain information that is purposely brief and succinct-just a simple statement or brief summary of the Daisy and each of the six Pyramids of Action. The Basic Tools are coloured orange.
The Support Tools™ provide more information and detail so that you know what to do to take action. Support Tools are coloured green.
The Reference Tools™ are lists of references that provide evidence for the information and recommended actions in the Basic and Support Tools. Reference Tools are coloured white.
The Glossary provides definitions and explanations of abbreviations and acronyms and is coloured white like the References.
By coloring the Levels icons this way, you can always tell whether you are using a Basic Tool, Support Tool or Reference Tool.

The Levels Pyramid™



THE FIGO PREVENTION OF UNSAFE ABORTION INITIATIVE

Unsafe abortion is a major cause of maternal mortality and morbidity. Every year some 19 million women around the world undergo induced abortions in unsafe conditions - of these, 97% take place in developing countries in Latin America, Africa and South Central Asia. An estimated 68,000 women die as a result of unsafe abortions, accounting for 13% of annual global maternal deaths, while hundreds of thousands of women suffer long-term complications.

> *"To date, most participating countries have achieved great progress, but mostly have understood and adopted the concept that abortion is a problem that cannot be ignored"*
>
> *Professor Anibal Faúndes*

Problems associated with haemorrhage, hospital admission, pelvic infection, and subfertility can be avoided by safe abortion services. Effective interventions for addressing the problem of unsafe abortion are well known and obstetricians and gynecologists are key actors in determining whether apropriate strategies are adopted and in the implementation of key interventions. Provision of safe abortion services within the legal framework is behind another FIGO project initiated in 2008: the 'Prevention of Unsafe Abortion Initiative'.

"The project, financially supported by an anonymous donor, involves 44 countries worldwide and is based on action plans - set on the basis of a preliminary situational analysis country by country - adopted as a country commitment by the government and the civil society," Professor Anibal Faúndes, Chair of the FIGO Working Group for the Prevention of Unsafe Abortion, said. These action plans include all or some of the four levels of prevention: primary, to reduce unintended pregnancies and abortions; secondary, to make unavoidable abortion safer; tertiary, for timely and correct treatment of abortion complications; and quaternary, to reduce its repetition.

A number of international and national agencies and NGOs are working in all or some of these prevention strategies. Consequently, they are contributing to the implementation of the plans of action in the different countries. The list of collaborating agencies is large and includes Amnesty International, Family Care International, UNICEF and WHO, amongst many others. The plans of action are dynamic and change over time. As some of the objectives are accomplished new ones are added to the plan or the same objective is expanded to serve larger populations or geographical areas.

"To date, most participating countries have achieved great progress, but mostly have understood and adopted the concept that abortion is a problem that cannot be ignored for its public heath significance and its meaning to womens lives, and consequently action needs to be taken to reduce its number and consequences. But this task is not an easy one and cannot be achieved in a short period of time. We are committed to continue working for the forseeable future and warmly welcome the collaboration of international agencies and NGOs, most of whom are already contributing to the implementation of the project in the different countries," Professor Faúndes ended.

EMERGENCY CONTRACEPTIVE PILLS: MEDICAL AND SERVICE DELIVERY GUIDELINES - THIRD EDITION 2012

The guidelines were created by a group of experts working with the International Consortium for Emergency Contraception. The first release appeared in 2000, the second in 2004. The third edition 2012 is endorsed by FIGO, whose representatives participated in reviewing the document.

Professor Ian Fraser is one of the FIGO experts involved in the review of the guidelines, he explained that "Despite the availability of highly effective methods of contraception, many pregnancies are mistimed or unwanted and may carry a high risk of morbidity and mortality, particularly in settings where safe abortion is not accessible. Many of these unintended pregnancies can be avoided using emergency contraception. Furthermore, emergency contraception provides a sense of security for those women who have experienced the life-changing trauma of sexual assault".

Emergency contraceptive pills, the most commonly used and most convenient form of emergency contraception, should be easily and widely available. Providers can be trained easily in the correct use, counselling and follow-up related to them. "The guidelines produced by the International Consortium for Emergency Contraception reflect the latest available evidence and are intended to assist family planning programmes and providers in assuring that the women they serve can use these regimens effectively and safely," Professor Adamson added.

FIGO PRESENTS RESULTS AND CONTINUATION OF NATIONAL PROJECTS TO SAVE MOTHERS AND NEWBORNS

In the bid to tackle Millenium Development Goal 5 'improvement of maternal health', the UN Secretary-General launched the '*Global strategy for Women's and Children's Health*' in 2012 to mobilise commitments by governments and civil society organisations to accelerate progress towards it.

"FIGO, well in advance to Mr Ban Ki-moon's avowal, set against this backdrop the Saving Mothers and Newborns Initiative, which resulted in great challenges and opportunities for 10 low and middle-resource countries in their quest to make a tangible difference in the reduction of maternal and newborn morbidity and mortality," said Dr André Lalonde, Chair of the FIGO Committee for Safe Motherhood and Newborn Health, presenting the results of the project at the FIGO2012 World Congress.

Dr Lalonde explained "Between 2006 and 2011 we worked with the associations of obstetricians, gynecologists and midwives of Haiti, Kosovo, Moldova, Nigeria, Pakistan, Peru, Uganda, Ukraine and Uruguay, with contributions from professional associations in high-resource countries through a structured north-south mentoring programme".

Each national project was indeed unique, focused on identified needs within the country and resulted in varied approaches and targets, ranging from clinical training through to legislative and policy change. "Significant results were achieved and led to direct improvements to maternal and newborn health outcomes. One of the most notable was the provision of clinical training to more than 2,000 health professionals, including traditional birth attendants, midwives, doctors and obstetricians," Dr Lalonde continued.

"As concrete examples: the Haiti project responded to the humanitarian disaster following the 2012 earthquake, through making our maternity centre one of the few in Port au Prince able to offer obstetrical care, thus preventing hundreds of maternal deaths; the Uruguay project - how to manage unsafe abortion in a country with very restrictive laws - set a model for many countries," he concluded.

GROUP B STREP INTERNATIONAL (GBSI) PRESENTS AND EXHIBITS AT FIGO TO REDUCE PERINATAL GBS INFECTIONS

Group B Streptococcal perinatal infections can be reduced 60%-85% by following known CDC protocols. To further promote prevention of Group B Strep disease in babies, Group B Strep International sent James A. McGregor, MDCM, and Ms. Marti Perhach, GBSI CEO and Cofounder, to the 2012 FIGO conference in Rome, Italy to present two distinct applied research papers: each one related to preventing GBS pregnancy and perinatal sepsis.

These two presentations demonstrated the functional connectedness of the upper and lower reproductive tracts. Patient ultrasounds using ultrasound contrast media placed in the vaginas of both a non-pregnant and pregnant woman were presented. It was clearly demonstrated that vaginal material (i.e., microorganisms, sperm, particles, or molecules) is promptly transported ("up sucked") into the uterus by uterine peristalsis.

This "up suck" phenomenon has been demonstrated many times previously, but here it was emphasized that bacteria including abnormal vaginal microflora, sexually transmitted infections (STI's), and HIV can be rapidly transported to the uterus.

In a 38 week gestation pregnant woman, it was demonstrated that manipulation of the cervix led to immediate transport of vaginal ultrasound contrast media in the lower uterine segment where it coated the fetal membrane "forebag" and decidua. This phenomenon is also well-known and is called the "Cervico-Uterine reflex."

GBSI's demonstration of this rapid transport of vaginal material supports the notion that stripping or sweeping of membranes to induce labor can massively inoculate the lower uterus with bacteria from the cervix and vagina, including GBS and E.coli.

A recent Cochrane analysis (Boulvain M, Stan C, Irion O. Membrane sweeping for induction of labour. Cochrane Database Syst Rev. 2005 Jan 25;(1):CD000451) concluded that membrane stripping (frequently painful, always invasive) was ineffective and could be reasonably avoided by standard medical induction of labor.

The presentations substantiated the US CDC-P's definition of prenatal-onset GBS (POGBS) sepsis leading to septic fetal death (septic stillbirth.) GBSI examined preventative strategies including Thomsen et al's (AC Thomsen, L Morup, KB Hansen. Antibiotic Elimination of Group-B Streptococci in Urine in Prevention of Preterm Labour. The Lancet, 1[8533]:591-593, 1987) screening for GBS bacteriuria at the first prenatal visit (penicillin treatment, followed by "test of cure" TOC) which reduced subsequent (0.5) prematurity, 0.5 PTB and premature rupture of membranes (pPROM 0.5.) GBS vaccination proposed by C. Baker et al could also be effective in prevention of stillbirth from POGBSS.

Additionally, Group B Strep International hosted a booth where they were able to give further information on these presentations and distribute patient materials including GBS brochures as well as status cards and tear sheets for GBS positive women to over 500 FIGO attendees. GBSI materials promote a checklist approach to help providers and their patients partner for better GBS disease prevention/ early identification.

GBSI also recorded heartfelt video testimonials by obstetricians from the UK, Saudi Arabia, Turkey, and Canada giving their support to universal GBS screening at 35-37 weeks gestation with selective intra-labor antibiotic prophylaxis (IAP) which is shown to prevent 80% of early-onset GBS sepsis (EOGBSS) according to the CDC-P's authoritative guidelines for preventing GBS disease worldwide.

For more information on these presentations, other prenatal infection resources, and/or to download complimentary materials, please visit www.groupbstrepinternational.org

THE FIGO CLASSIFICATION OF CAUSES OF ABNORMAL UTERINE BLEEDING

In 2006 FIGO established a FIGO Menstrual Disorders Working Group as it had become increasingly clear that there was considerable confusion regarding several aspects of the very common symptom of abnormal uterine bleeding (AUB). This Group has focused on the thorny problems of vague terminologies and the development of a definitive classification of the causes of abnormal bleeding. These are critical issues for international research and communication about abnormal bleeding, as well as providing a sound platform for individual patient management.

The initial focus was on development and clarification of simplified terminologies around the symptoms and diagnoses underlying abnormal bleeding, including use of terms which women and men in the community can understand. The second intention was to develop a comprehensive and clinically relevant classification system which was presented in a format suitable for straightforward clinical use, as well as allowing more detailed categorisation for specialist and research needs.

Professor Ian Fraser, Chair of the FIGO Working Group on Menstrual Disorders, spoke about the 'FIGO Classification of Causes of Abnormal Uterine Bleeding' at the FIGO2012 World Congress. He explained: "Its purpose is to provide a structured context for clinical research, medical education, and the provision of clinical care for women with abnormal uterine bleeding. It has been designed to be flexible, suitable for regular review and revision and adaptable for use at the primary care, specialist and clinical investigator levels. The system eliminates the use of vague and undefined diagnostic and symptomatic terms like 'dysfunctional uterine bleeding' and 'menorrhagia', therefore allowing improved communication about menstrual symptoms, coordinated research planning and improved diagnostic precision, critical elements of any strategy designed to enhance the standard of care for women with this condition,".

The FIGO-approved classification should assist in providing a solid basis for the standardisation of international research and clinical manuscripts addressing the diagnosis, pathogenesis and management of AUB. It is recognised that, from time to time, new research will lead to a need for greater precision or modification of initial recommendations.

Hence, the FIGO classification is regarded as a flexible "living" document that should undergo review and consideration for modification at regular intervals. It is suggested that discussion of the practical use and clarity of the classification should initally occur at 3-yearly intervals - in line with each FIGO World Congress.

Management of Recurrent Cystitis in Women: Role of the Non-Antimicrobial Prophylaxis

Summary of Presentations given at OM Pharma Lunch Symposium at the XX FIGO World Congress in Gynecology and Obstetrics, Rome, 9th October 2012

Matteo Bassetti[1], Diana Mansour[2] and Harald Meden[3]

1. Head Infectious Diseases Division, Santa Maria Misericordia University Hospital, Udine, Italy;
2. Consultant in Community Gynecology and Reproductive Healthcare, Newcastle upon Tyne, UK;
3. Professor in Obstetrics and Gynecology, University of Gottingen, Germany, Head of Surgical Diagnostics and Treatment, Paracelsus Hospital, Zurich, Switzerland.

Disclosure: The authors are global advisors of OM Pharma company, Meyrin, Switzerland.
Acknowledgements: Assistance was provided by Sarah Richardson, Trilogy Writing and Consulting, Norfolk, UK.
Support: The publication of this article was funded by OM Pharma. The views and opinions expressed are those of the authors and not necessarily those of OM Pharma.

Citation: *European Medical Journal - Gynecology and Obstetrics*, 2012;1:26 –33

Alarming Increase of Resistance to Antimicrobial Agents in Pathogens Responsible for Urinary Tract Infections

Prof. Dr. Matteo Bassetti

Fifty years ago there were few, if any, effective antibiotics and there is a growing fear that we are returning to the same situation. The paradox is that the *miracle* drugs (antibiotics) have destroyed the *miracle* (successful treatment of infection). This situation has occurred because over the last 50 years, antibiotics have been overused or misused, and the considerable incidence of illegal over-the-counter sales in the European Union have contributed to this inappropriate use of antibiotics.[(1)] Thus, bacterial resistance has grown, generating circumstances where almost all antibiotics in the future may be ineffective against today's super bugs.

The difficulty is that resistance is not always reversible and there is a continuing need for new antimicrobial agents which are active against resistant pathogens[(2)]. Unfortunately companies are not investing in producing new antibiotics and consequently antibiotic options have declined.

The production of new antibiotics has steadily decreased from 16 new antibiotics discovered between 1983 and 1987 to almost none within the last 3 years (Fig.1).[(3)] A practical solution to moderate the course of this trend is to reduce antibiotic use. Conventional wisdom suggests that this might be achieved by reducing the number of infections, and where antibiotics have to be used, 'use less, less is better' should be the theme. Possible interventions include targeting, improving compliance, restricting prophylaxis to where it is of proven value, continuing education of health care providers and the public, and reduction of excessive use. Less conventional approaches might involve application and better

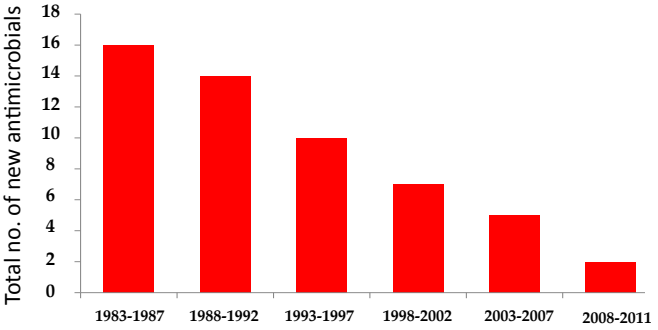


Figure 1. New antibacterial agents approved by the FDA according to the IDSA Public Policy, 2011.

understanding of immunomodulating agents and advances in chronobiology.[4]

The 3 main classes of antimicrobials that can be used to treat urinary tract infection (UTI) are third-generation cephalosporins, fluoroquinolones and carbapenems. 90% of UTI are caused by gram-negative bacteria, usually *E. coli*. Gram-negative bacteria have become increasingly resistant to available antibiotic drugs, limiting the choice of treatment. This is due to extended-spectrum beta-lactamases (ESBLs) - enzymes that are resistant to most beta-lactam antibiotics, including penicillins, cephalosporins and carbapenems (Fig.2). There is a significant incidence globally of ESBL-producing gram-negative bacilli (GNB) such as *E.coli*, *K. pneumonia* and *K. oxytoca* that are resistant to beta lactamases.[5] *E. coli* has been shown to be resistant to cephlosporins and fluoroquinolones leaving the use of carbapenems as the only antimicrobial treatment currently available.[6]

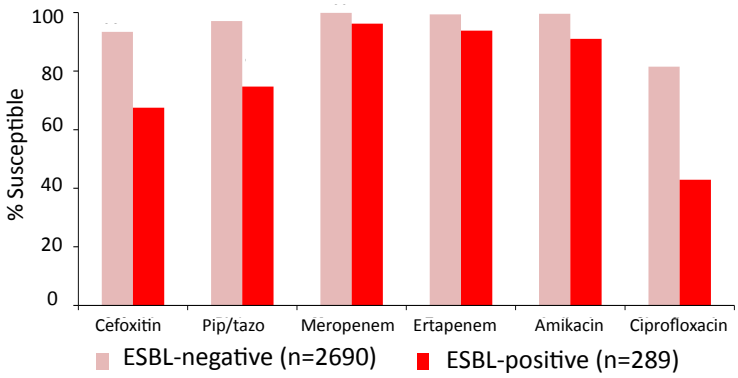


Figure 2. Gram negative bacteria susceptibility to antibiotics: results from the Study for Monitoring Antimicrobial Resistance Trends (SMART)

However, the incidence of carbapenem resistant strains worldwide is increasing. In the past 10 years *Klebsiella pneumoniae* carbapenemase has become widely disseminated, resulting in an increase in carbapenemase-resistant *Enterobacteriaceae* (CRE).[7] CRE produce Verona integron-encoded metallo-β-lactamase and New Delhi metallo-β-lactamase, which are now distributed globally. Metallo-β-lactamases have complex patterns of multi-drug resistance and their spread presents a major health challenge, particularly as mortality rates have increased due to these types of resistant strains.[8,9,10,11,12]

Antibiotic sales in the community represent > 70% of all antibiotic sales. The largest use of antibiotics is for minor respiratory infections (frequently viral) and UTI, which are often self-limiting and self-healing, rendering the usefulness of antibiotics dubious. Antibiotics may be overused as a result of patient demand, and therefore the public should be educated about the nature of infection, the real benefit of antibiotic treatment, and the different solutions that are available to treat minor infections. To counteract the increasing problem of resistance, a multi-factorial strategy (antimicrobial stewardship) is required. This should include benchmarks and education, reduce resistant reservoirs, introduce new drugs and vaccines, and improve diagnostics and infection control.

In conclusion, there is a progressive increase in antibiotic resistance. Infection control measures are useful in delaying resistance, but very rarely capable of reducing the incidence of nosocomial infections involving multi-drug resistant (MDR) organisms. A second antibiotic crisis appears inevitable in the short term because of MDR GNB infections. New therapeutic strategies will likely become available in the next decade. In recurrent UTI, the increasing resistance to many antibiotic families makes it imperative, more than ever, that alternative preventative approaches are used that spare antibiotics.

Prevention of Recurrent Cystitis: Alternative Strategies to Antimicrobials

Dr. Diana Mansour

UTI, mainly cystitis, are among the most prevalent infectious diseases of bacterial origin. Women have a 1 in 3 life time risk of UTI where as men only have a 1 in 20 life time risk, and every year, 5% of women present with frequency and dysuria.[13]

Cystitis is a benign condition but has a detrimental effect on quality of life. Women suffer extensively from pain, discomfort, inconvenience, and disturbance of their daily life. Furthermore, they live with the constant anxiety that they are going to suffer from a new undesirable infection.

Recurrent cystitis is defined as either ≥ 2 acute infections in 6 months or ≥ 3 infections in 12 months.

Recurrent cystitis must be diagnosed by urine culture since relapses or re-infections are frequent in women. 40% of women (980 million) will have a UTI in their lifetime; about 25% of them (245 million) will experience another episode within 6 months, and 44% within 12 months. Therefore, in total about 10% of women suffer from recurrent UTI.[14,15,16]

The most common gram-negative bacterium involved is *E-coli*, which is the cause of around 77% of all UTI (Fig.3).[17] *E-coli* adheres to the uroepithelium, invades very easily, and multiplies quickly causing local inflammation. It is likely that if a person has had one *E-coli* infection they will suffer a recurrence within the following 6 months.[18]

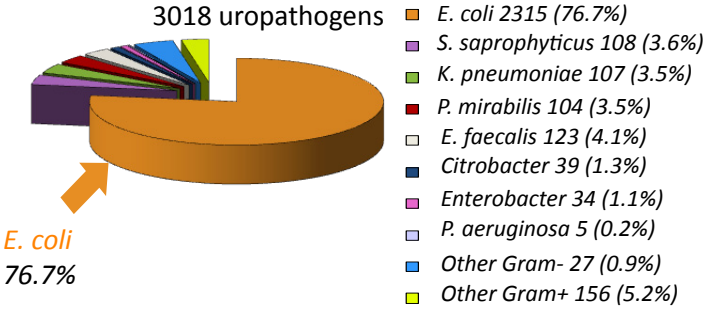


Figure 3. Antimicrobial Resistance Survey on Cystitis (ARESC) on bacterial isolates in patients' urine in Europe and Brazil

To determine and potentially treat a patient who presents with suspected cystitis, the European Association of Urology guidelines (EAU) recommend that the patient must present with 2 of the following 3 clinical symptoms: frequency, dysuria, and/or lower abdominal burning.[19] Routine assessment should also include exclusion of sexually transmitted infection, particularly if there is vaginal discharge, and urinalysis for nitrites and leucocytes. However, the microorganism should only be identified by urine culture in cases of pyelonephritis, recurrent cystitis, and pregnancy, as advised by the European Committee for Antimicrobial Susceptibility.

Antibiotics are an effective treatment for UTI but bacteria can re-establish, causing recurrent cystitis. Whether this is due to persistent bacteria or re-infection is unknown. Treatment of acute infection only is not sufficient. When recurrence is a problem, a long term solution should be considered and prevention taken into account.

Non-antimicrobial measures in the form of lifestyle changes can reduce the risk of recurrent cystitis. If cystitis is related to sexual intercourse, recurrence can be prevented by avoiding the use of diaphragms or spermicide, voiding before and after intercourse and, in post-menopausal women, using a lubricant if they experience vaginal dryness.

The EAU guidelines for non-antimicrobial prophylaxis of UTI suggest considering the use of oestrogens in post-menopausal women, using probiotics (*Lactobacillus sp.*) orally and/or intravaginally, ingesting oral cranberry products and oral/injectable immunoactive prophylaxis.[20]

The rationale for the use of oestrogens in post-menopausal women is that the female genital and lower urinary tract is potentially receptive to the action of oestrogen at all times. This is because the female genital and lower urinary tract is derived from the uro-genital sinus which has oestrogen receptors in the urethra, urethral sphincter, trigone and the muscles of the pelvic floor. Vaginal oestrogen increases the number of vaginal lactobacilli, which reduces the recurrence of UTI. Current evidence shows that topical oestrogen reduces the prevalence of UTI from 23.7% to 6%, reduces sensory bladder symptoms (frequency, urgency, nocturia) from 47.4% to 9.4%, reduces dysuria from 42.2% to 10.7%, improves operative results after prolapse repairs and trans vaginal tape procedures, and may have a synergistic role with α-adrenergic agonists.[21,22,23,24,25] The EAU guidelines give a recommendation Grade C for the use of vaginal oestrogens in post-menopausal women with recurrent cystitis.[26] However, oral oestrogen has been shown to be less effective than topical oestrogen. Four studies involving 2798 women showed that oral oestrogens did not reduce UTI compared with placebo. Oral oestrogen is not as effective because it does not reach all parts of the genital and lower urinary tract.[27]

Depletion of vaginal lactobacilli is associated with UTI risk which suggests, based on the principle of bacterial interference, that repletion may be beneficial. A recent randomised placebo-controlled phase 2 trial using lactobacilli prophylactically following treatment with antibiotics reduced recurrent UTI by 50%.[28] Conversely, a double blind non-inferiority trial comparing trimethoprim-sulfamethoxazole (TMP-SMX) with the lactobacilli *L. Rhamnosus* GR-1 and *L. Reuteri* RC-14 to prevent recurrent cystitis found that after 12 months, the mean number of UTI was 2.9 in the antibiotic group and 3.3 in the lactobacilli group,

showing that *L. rhamnosus* GR-1 and *L. reuteri* RC-14 were inferior in the prevention of UTI compared with TMP-SMX. However, it should be noted that unlike TMP-SMX, the use of lactobacilli did not increase antibiotic resistance.[29] The EAU guidelines for the use of probiotics (2012) state that accessibility of clinically proven probiotics for UTI prophylaxis is not universal. Only *Lactobacillus sp* strains that show benefit should be used for prophylaxis; when commercially available these products can be used once or twice weekly.

Current evidence favours the antibacterial role of cranberry's natural polyphenols or tannins. Cranberries (*Vaccinium macrocarpon*) contain tannin-like compounds called proanthocyanidins (PACs). PACs inhibits P-fimbrial adhesion of *E. coli* to uroepithelial cells. Dosage should be at least 36 mg PAC per day to prevent UTI. There are several products availabe including juices and capsules, but the dosage is not standardised which makes studies difficult to compare.[30,31] Although comparison of studies is difficult, cranberry prophylaxis has been shown to be effective.[32]

Kontiokari *et al* studied women receiving cranberry juice for 6 months, lactobacillus GG drink for 12 months, or no intervention. At the 12 month follow-up point, the difference between the groups was significant (P=0.023 at 6 months, 0.048 at 12 months). Occurrence of UTI was significantly lower in the cranberry group than in the control group (P=0.014 at 6 months, 0.052 at 12 months) showing a 25% recurrence in the cranberry group and 50% in the control group.[33]

Cranberry-containing products have also been shown to prevent UTI in susceptible populations. A systematic review and meta-analysis of 10 trials (1494 subjects) showed that the random-effects pooled risk ratio (RR) for cranberry users versus nonusers was 0.62 (95% CI, 0.49-0.80). Cranberry products were effective in women with recurrent UTI (RR, 0.53; 95% CI, 0.33-0.83), in female populations (RR, 0.49; 95% CI, 0.34-0.73), in children (RR, 0.33; 95% CI, 0.16-0.69), in cranberry juice drinkers (RR, 0.47; 95% CI, 0.30-0.72), and in those taking cranberry-containing products more than twice daily (RR, 0.58; 95% CI, 0.40-0.84). This shows a reduction in UTI in women overall, but is even more effective in women who suffered from recurrent UTI (risk ratio showed 50% reduction).[34]

There are contradictory results concerning the use of cranberries in UTI prophylaxis, however the EAU guidelines (2012), whilst acknowledging the controversy, state that cranberry juice may still be an interesting prophylaxis, and give it a Grade C recommendation. Despite the lack of pharmacological data and the small number of weak clinical studies, evidence suggests that cranberry products are useful in reducing the rate of lower UTI in women, and recommend the daily consumption of cranberry products to be a minimum of 36 mg/day PAC.[35]

If non-antimicrobial measures have been unsuccessful, antibiotic prophylaxis should be considered. This can be continuous antimicrobial therapy, a reduced post-coital dose of antimicrobials, or repeated short-term therapy. Continuous low dose antibiotics are often given, which increase the risk of resistance. Short high dose courses should be given to symptomatic women (or a one off post coital dose) to reduce the chance of a recurrent UTI.

In conclusion, there are several alternative therapies currently available for the prevention of recurrent cystitis that do not increase antibiotic resistance. What is the place of immunoactive prophylaxis?

Immunoactive Prophylaxis in the Management of Recurrent Cystitis

Prof. Dr. Harald Meden

Antibiotic resistance is causing a serious problem in the treatment of recurrent cystitis. The European Guidelines on Urological infection (EAU) recommend that the treatment of recurrent cystitis adheres to the following principles: initially general prophylaxis should be considered; followed by non-antimicrobial prevention (in order to avoid antibiotic use); finally, if non-antimicrobials have been unsuccessful, antimicrobial prevention should be used.[36]

In line with the EAU guidelines, immunoactive prophylaxis is a non-antimicrobial option that should be considered in the management of recurrent cystitis. Recurrences of infection or chronic infections can be triggered by any reduction in the efficiency of the host's immune response, e.g. environmental factors, overuse of antibiotics, age or genetic factors. Therefore, the patient's underlying immune status

is fundamental in the development of recurrent urinary tract infections (UTI). Any intervention aimed at enhancing the immune system and the host's defences in the urinary tract represents an excellent opportunity for preventive medicine.[37]

The immune system can also be stimulated to target the urinary tract. Uropathogenic *E. coli* can be one of thousands of different clones or strains. There are two immunoactive strategies that can be used to target *E. coli*, a single antigen (e.g. Type 1 fimbriae) or several antigens (e.g. extract of inactivated uro-pathogens). A mixture of oral antigens can stimulate the immune system in the urinary tract as activated cells and antibodies in the mucosa associated lymphoid tissue (MALT) in the gut can re-circulate to other MALT via the systemic blood circulation or the lymphatic system where they act as a mechanism of defence against uro-pathogens (Fig.4). OM-89 (Uro-Vaxom®) is an oral immunoactive product manufactured from 18 selected and standardised strains of *E. coli* known to be the most common uropathogens responsible for cystitis.

OM-89's biological activity has been demonstrated in several pre-clinical *in vitro* and *in vivo* studies specifically in the urinary tract.[38,39,40,41,42,43] Furthermore, its clinical efficacy and safety has been tested in five randomised double blind placebo controlled clinical studies of 6 months' duration and confirmed by other long-term studies (12 months duration) and a meta-analysis.[44,45,46,47,48]

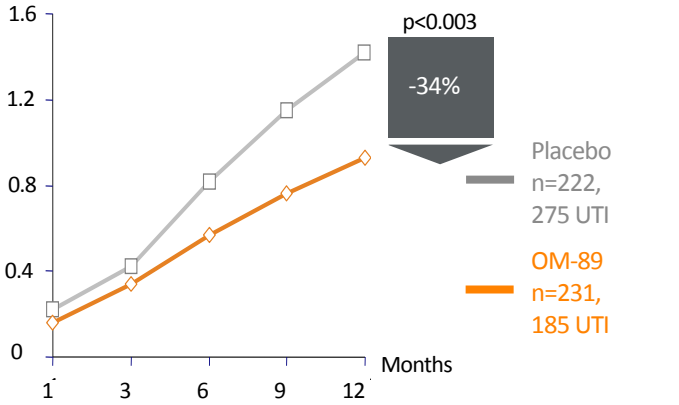


Figure 5. Cumulative relapse rate of UTI by visit (ITT population; p<0.003)

OM-89 has been shown to reduce the mean number of UTI compared with placebo by up to 50% in several studies and has been shown to have an antibiotic sparing effect with a reduction in mean number of days of antibiotic intake of up to 67%.[49] In a multicentre randomised placebo controlled trial (12 months' duration), 453 women suffering from recurrent cystitis were given OM-89 once daily for 3 months, and following 3 months' observation were given a booster regimen for a further 3 months. The cumulative mean rate of UTI was reduced in the OM-89 group by 34% (statistically significant) compared with placebo at the end of the study (Fig.5).[50] A meta-analysis of 5 double blind placebo controlled studies pooled data from approximately 1000 patients suffering from recurrent UTI. The analysis showed that OM-89 (*verum*) reduced the mean number of UTI by 36% compared with placebo at 6

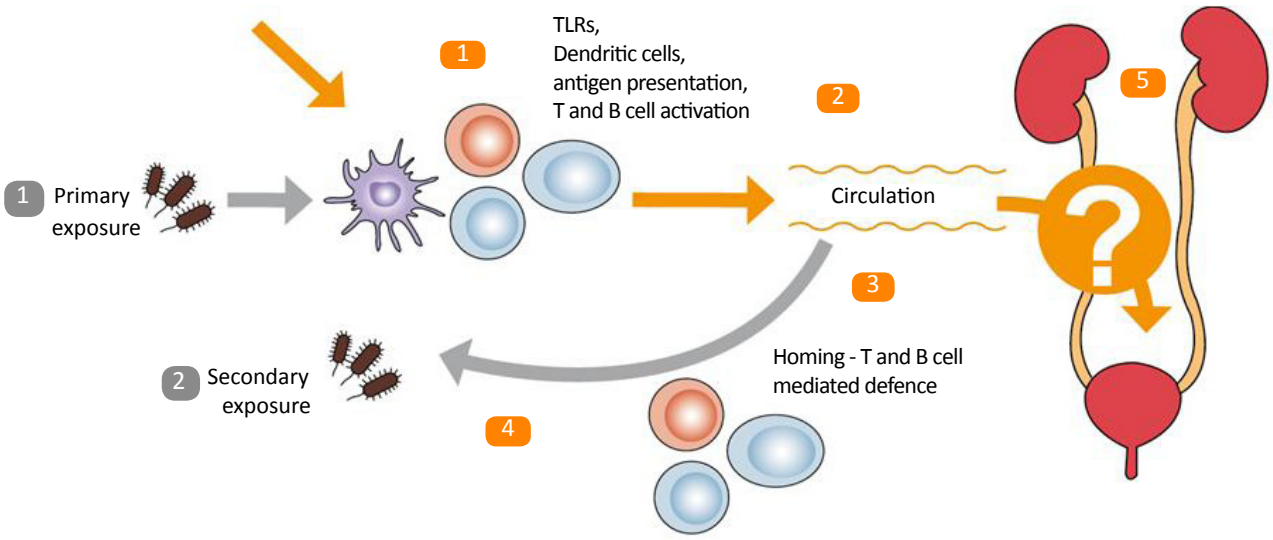


Figure 4. Hypothesis of activation of immune system effectors in the Mucosa Associated Lymphoid Tissue (MALT) in the gut and the bladder via systemic re-circulation, after oral ingestion of antigens entering OM-89 composition

months and by 39% at the end of all studies (including 12 months' data: Bauer *et al*. data not shown) (Fig.6). Furthermore, the same analysis showed that studies with the largest number of UTI in the placebo group where those that demonstrated the largest benefit from OM-89 prophylaxis. This suggests that the higher the risk of bladder infections, the greater the benefit of prophylaxis with OM-89. The distribution of post baseline UTI per patient was in favour of OM-89 and this was statistically significant (Fig.7). The clinical effect was associated with a significant reduction of antibacterial use (data not shown); the meta analysis showed that OM-89 was well tolerated with a safety profile comparable with placebo.[51]

OM-89 has also been tested in special target populations. Pilot studies have been conducted in children, post-menopausal women, pregnancy, and patients with spinal cord injury. The results have shown OM-89 to have a good safety profile[52] in these special populations compared with baseline values. In particular, in pregnant women the incidence of UTI was reduced by 62% compared with baseline values, only 3.2% of patients included in the study experienced slight side effects of nausea and heartburn, though the authors believed that this was possibly associated with pregnancy, and all new-born infants were born alive and healthy with normal Apgar scores.[53]

In children UTI were reduced by 70%; in post-menopausal women the reduction was 65% compared with baseline values. In a randomised cross-over study versus placebo in paraplegic patients there was a 50% reduction in mean bacteriuria over a 6 month period.[54,55,56,57]

Recurrent UTI can have a detrimental effect on the patient's quality of life. The Harmony study involving 575 patients showed that at entry 62% of patients presented with a global Hospital Anxiety and Depression Scale (HAD) score indicative of minor anxiety or depression. At the end of the survey, a 59% decrease in mean lower UTI was observed, along with a 36% decrease in anxiety state, 25% decrease in depression score and a decrease of 32% in overall HAD scores, all of which were highly significant ($p<0.0001$) compared with baseline. These improvements in quality of life indicators significantly correlated ($p<0.0001$) with the reduction in cystitis (Table 1). [58]

Recurrent cystitis is common and is a real burden for women, who experience unbearable pain and the anxiety of further cystitis. Treating repeated acute infections alone is suboptimal in providing relief for these patients, and does not assure successful disease management, causing women to continue returning for treatment. In order to

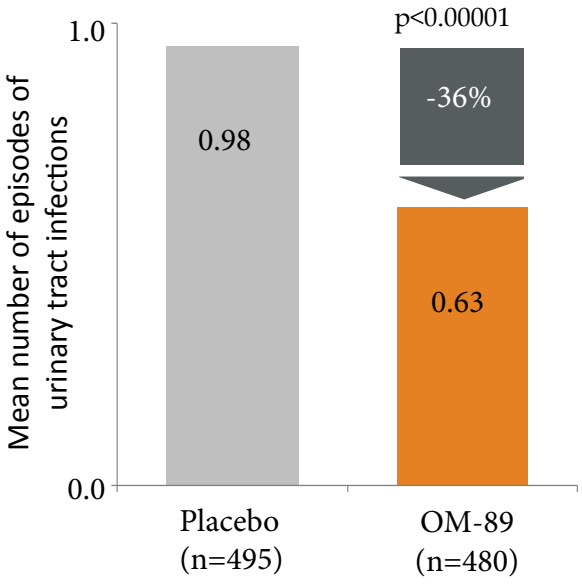


Figure 6. Mean number of UTI at 6-months in OM-89 and placebo groups (test for heterogeneity, p=0,002; test for overall effects, p<0,00001)

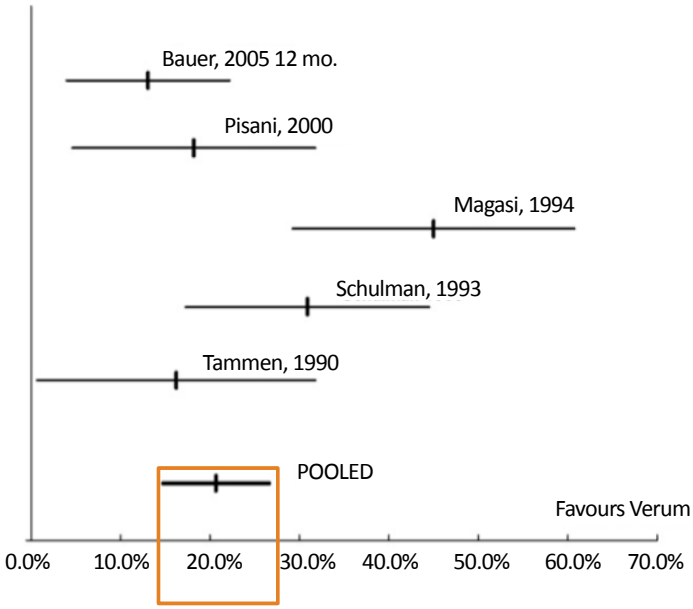


Figure 7. Percentage of patients without urinary tract infections: difference between OM-89 and placebo at the end of the studies

Correlations	Day 0		Day 180	
	Number of UTI Mean (Std Dev)	Coefficient of correlation (p value)	Number of UTI Mean (Std Dev)	Coefficient of correlation (p value)
Depression score and number of urinary episodes	2.8 (1.2)[1]	coeff= 0.14027 (p=0.0023)	1.6 (1.2)[1]	coeff= 0.28136 p<0.0001
Anxiety score and number of urinary episodes	2.7 (1.3)[2]	coeff= -0.02349 (p=0.6081)	1.5 (1.3)[2]	coeff= 0.29786 p<0.0001
Global HAD score and number of urinary episodes	2.7 (1.3)[3]	coeff= 0.06010 (p=0.1934)	1.1 (1.1)[3]	coeff= 0.32234 p<0.0001

Key: coeff=coefficient of correlation; Std Dev=standard deviation; UTI=urinary tract infection

1. Number of UTI for patients with a depression score ≥ 8 at baseline
2. Number of UTI for patients with an anxiety score ≥ 8 at baseline
3. Number of UTI for patients with depression and anxiety scores < 8 at baseline were excluded

Table 1. Correlation between anxiety and depression scores and UTI number at Day 0 and Day 180

improve treatment outcomes and patients' quality of life, an effective preventative treatment, validated by evidence-based medicine, is required. Several strategies are available to prevent recurrent bladder infections, including antimicrobial prophylaxis. The alarming increase in antibiotic resistance and the poor armamentarium against gram-negative bacteria necessitate alternatives to antibiotics.

OM-89 is such an alternative. It has been shown to be more effective than placebo in several randomised trials and meta-analysis. Furthermore, it is recommended in the EAU guidelines for immunoprophylaxis in women with recurrent cystitis with the highest grade of recommendation (Grade B) and the top level of scientific evidence (1a).

References

1. ***Plachouras D,Kavatha D, Antoniadou A, et al.,*** *Dispensing of antibiotics without prescription in Greece, 2008: another link in the antibiotic resistance chain. Euro Surveill, 2010;15(7):19488*

2. ***Hamilton-Miller JM,*** *Antibiotic resistance from two perspectives: man and microbe, Intl J Antimicrob Agents, 2004;23:209-212*

3. ***Infectious Diseases Society of America (IDSA), Spellberg B, Blaser M, Guidos RJ, et al.,*** *Combating antimicrobial resistance: policy recommendations to save lives, Clin Infect Dis, 2011;52(Suppl 5):S397-S428*

4. ***Hamilton-Miller JM,*** *Antibiotic resistance from two perspectives: man and microbe, Intl J Antimicrob Agents, 2004;23:209-212*

5. ***Hamilton-Miller JM,*** *Antibiotic resistance from two perspectives: man and microbe, Intl J Antimicrob Agents, 2004;23:209-212*

6. ***Rossi F, Baquero F, Hsueh PR, et al.,*** *In vitro susceptibilities of aerobic and facultatively anaerobic Gram-negative bacilli isolated from patients with intra-abdominal infections worldwide: 2004 results from SMART (Study for Monitoring Antimicrobial Resistance Trends), J Antimicrob Chemothe, 2006;58(1):205-210*

7. ***Gupta N, Limbago BM, Patel JB, et al.,*** *Carbapenem-resistant Enterobacteriaceae: epidemiology and prevention, Clin Infect Dis, 2011;53(1): 60-7*

8. ***Cornaglia G, Giamarellou H, Rossonili GM,*** *Metallo-ß-lactamases: a last frontier for ß-lactamases? Lancet Infect Dis, 2011; 1:381-93*

9. ***Qureshi ZA, Paterson DL, Potoski BA et al.,*** *Treatment outcome of bacteremia due to KPC-producing Klebsiella pneumonia: superiority of combination antimicrobial regimens, Antimicrob Agents Chemother. 2012; Jan 17 ePub*

10. ***Bergamasco MD, Barroso Barbosa M, de Oliveira Garcia D, et al.,*** *Infection with Klebsiella pneumonia carbapenemase (KPC)-producing K. pneumoniae in solid organ transplantation, Transplan Inf Dis. 2011;Oct 28 ePub.*

11. ***Qureshi et al****. Clin Micro Infect. 2011; Aug 25 ePub*

12. ***Marchaim D, Chopra T, Perez F, et al.,*** *Outcomes and genetic relatedness of carbapenem-resistant enterobacteriaceae at Detroit medical center, Infect Control Hosp Epidemiol, 2011; 32(9):861-71*

13. ***www.patient.co.uk.***

14. ***Foxman B,*** *Recurring urinary tract infection: incidence and risk factors, Am J Public Health, 1990;80(3):331-333*

15. ***Foxman B,*** *Epidemiology of urinary tract infections: incidence, morbidity and economic costs, Am J Med, 2002, 113, Suppl 1A:5S-13S*

16. ***Sivick KE, Morbley HL,*** *Waging war against uropathogenic Escherichia coli: winning back the urinary tract, Infection and Immunity, 2010;78(2):568–585*

17. ***Naber KG, Schito G, Botto H, et al.,*** *Surveillance study in Europe and Brazil on clinical aspects of Antimicrobial Resistance Epidemiology in Females with Cystitis (ARESC): implications for empiric therapy,. European Urology, 2008; 54(5):1164-75*

18. ***Grabe M, et al.,*** *European Association of Urology Guidelines on Urological Infections, 2012. www.uroweb.org*

19. ***Grabe M, et al.,*** *European Association of Urology Guidelines on Urological Infections, 2012. www.uroweb.org*

20. ***Grabe M, et al.,*** *European Association of Urology Guidelines on Urological Infections, 2012. www.uroweb.org*

21. ***Hilton,*** *Int Urogynecol J, 1990*

22. ***Cardozo L, Lose G, McClish D, et al.,*** *A systematic review of oestrogens for recurrent urinary tract infections: third report of the hormones and urogenital therapy (HUT) committee, Int Urogynecol J Pelvic Floor Dysfunct, 2001;12(1):15-20*

23. ***Simunic V, Banovic I, Ciglar S, et al.,*** *Local oestrogen treatment in patients with urogenital symptoms, Int J Gynaecol Obstet, 2003;82(2):187-97*

24. **Moehrer et al**, 2004,

25. **Raz R, Stamm WE**, A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections, N Engl J Med, 1993;329(11):753-6

26. **Grabe M, et al**., European Association of Urology Guidelines on Urological Infections 2012. www.uroweb.org

27. **Perrotta C, Aznar M, Mejia R, et al**., Oestrogens for preventing recurrent urinary tract infection in postmenopausal women, Cochrane Database Syst Rev, 2008;(2):CD005131

28. **Stapleton AE, Au-Yeung M, Hooton TM, et al.**, Randomized, placebo-controlled phase 2 trial of a Lactobacillus crispatus probiotic given intravaginally for prevention of recurrent urinary tract infection, Clin Infect Dis, 2011;52(10):1212-7

29. **Beerepoot MA, ter Riet G, Nys S, et al.**, Lactobacilli vs antibiotics to prevent urinary tract infections: a randomized, double-blind, non inferiority trial in postmenopausal women, Arch Intern Med, 2012;172(9):704-12

30. **http://foodspeople.com**/e-coli-(H Botto, personal communication)

31. **Grabe M, et al.**, European Association of Urology Guidelines on Urological Infections, 2012. www.uroweb.org

32. **Kontiokari T, Sundgvist K, Nuutinen M, et al**., Randomised trial of cranberry-lingonberry juice and Lactobacillus GG drink for the prevention of urinary tract infections in women, BMJ, 2001;322(7302):1571

33. **Kontiokari T, Sundgvist K, Nuutinen M, et al**., Randomised trial of cranberry-lingonberry juice and Lactobacillus GG drink for the prevention of urinary tract infections in women, BMJ, 2001;322(7302):1571

34. **Wang CH, Fang CC, Chen NC, et al.**, Cranberry-containing products for prevention of urinary tract infection in susceptible populations: a systematic review and meta-analysis of randomized controlled trials, Arch Intern Med, 2012;172(13):988-96

35. **Grabe M, et al**., European Association of Urology Guidelines on Urological Infections 2012. www.uroweb.org

36. **Grabe M, et al.**, European Association of Urology Guidelines on Urological Infections 2012. www.uroweb.org.

37. **Mannhardt W**, [What is the cause of recurrent urinary tract infection?] article in German. Monatsschr kinderheilkd. 1992;140(12):842–846

38. **OM-89** Summary of Product Characteristics-Swissmedic 2006

39. **Bessler WG, Kleine B, Martinez Alanso C, et al.**, Biological activity of bacterial components: bacterial extracts and defined bacterial cell and wall components as immunomodulators, Lung, 1990;168 Suppl:707-715

40. **Bessler WG, Beck P, Konetznick U, et al.**, Biological activity of bacterial surface components. Immunogenicity and immunomodulatory properties of a bacterial extract from Escherichia coli, Arzneimittelforschung, 1991;41(3):274-9.

41. **Huber M, Krauter K, Winklemann G, et al.**, Immunostimulation by bacterial components: II. Efficacy studies and meta-analysis of the bacterial extract OM-89, Int J Immunopharmacol, 2000;22(12):1103-11

42. **Bessler WG, vor dem Esche U, Zgaga-Griesz A, et al.**, Immunostimulatory properties of the bacterial extract of OM-89 in vitro and in vivo, Arzneimittelforschung, 2010;60(6):324-329

43. **Lee SJ, Kim SW, Cho YH, et al.**, Anti-inflammatory effect of an Escherichia coli extract in a mouse model of lipopolysaccharide-induced cystitis, World J Urol, 2006; 24(1):33-38

44. **Frey CH, Obolensky W, Wyss H**, Treatment of recurrent urinary tract infections: efficacy of an orally administered biological response modifier, Urol Int, 1986;41(16):444-446

45. **Tammen H**, Immunobiotheray with Uro-Vaxom in recurrent urinary tract infection. The Germ Urinary Tract Infection Study Group, Br J Urol 1990;65(1):6-9

46. **Schulman CC, Corbusier A, Michiells H et al**., Oral immunotherapy of recurent urinary tract infections: a double-blind placebo-conrolled multicenter study. J Urol, 1993; 150(3):917-21

47. **Magasi P, Pancovics J, Illes A, et al.**, Uro-Vaxom and the management of recurrent urinary tract infection in adults: a randomized multicenter double-blind trial, Eur Urol, 1994;26(2):137-40

48. **Pisani E et al**. OM pharma data on file 1992 (quoted in Chiavaroli C, Moore A, An hypothesis to link the opposing immunological effects induced by the bacterial lysate OM-89 in urinary tract infection and rheumatoid arthritis, BioDrugs, 2006;20(3):141-9)

49. **Schulman CC, Corbusier A, Michiells H et al.**, Oral immunotherapy of recurent urinary tract infections: a double-blind placebo-conrolled multicenter study. J Urol, 1993; 150(3):917-21

50. **Bauer H.W, alloussi S, Egger G,et al.**, A long-term, multicenter, double-blind study of an Escherichia coli extract (OM-89) in female patients with recurrent urinary tract infections, Eur Urol, 2005;47(4):542-548

51. **Naber K.G, Cho Y-H, Matsumoto T, et al.**, Immunocactive prophylaxis of recurrent urinary tract infections : a meta-analysis, Int J Antimicrob Agents 2009;33:111-119

52. **Baertschi** Int J Immunoth 2003; 19: 1, 25-31

53. **Naber K.G, Cho Y-H, Matsumoto T, et al.**, Immunocactive prophylaxis of recurrent urinary tract infections : a meta-analysis, Int J Antimicrob Agents 2009;33:111-119

54. **Czerwionka – Szaflarska M, Pawlowska M.** Influence of Uro-Vaxom on sIgA level in urine in children with recurrent urinary tract infections, Arch Immunol Ther exp 1996; 44:444-6,

55. **Lettgen B.** Current therapeutic Research 1996;57 (6):464-75

56. **Popa G et al**. MÜNCHENER MEDIZINISCHE WOCHENSCHRIF T. 1996;138:713-716

57. **Hachen HJ,** Oral immunotherapy in paraplegic patient with chronic urinary tract infections: a double-blind , placebo-controlled trial, J. Urol, 1990;143(4):759-763

58. **Renard J et al.**, Recurrent lower urinary tract infections have a detrimental effect on patient quality-of-life, Int J Gynecol Obstet 2012;119S3:S531-S867

Primary Screening for Human Papillomavirus in Cervical Cancer Prevention

Mieke Vandecasteele[1], Willy Poppe[2]

[1]Resident , [2]Professor, M.D., Ph.D. Department of Gynecology and Obstetrics
Catholic University of Leuven

Prof. Dr. Willy Poppe

Abstract

Acquisition of a high risk Human Papillomavirus (hr HPV) infection is a necessary step in the pathogenesis of cervical cancer. Hr HPV detection has a significantly higher sensitivity in the early detection of cervical precancerous lesions than cytology, but a lower specificity. For primary screening tests higher sensitivity is preferential to a higher specificity, since the goal is to prevent as much as possible. The large majority of cervical cancer screening programs in Europe are still cytology based. A switch from cytology based to hr HPV DNA based screening is being implemented in several pilot settings.

Since the specificity of hr HPV-testing in primary screening settings is lower compared to cytology, triage of hr HPV positive women before referral to colposcopy is necessary. Triage with cytology, proliferation proteins, detection of methylated DNA regions and viral load slope plot is being investigated.

Different subgroups of patients would benefit from different screening programs. Hr HPV based screening is preferential in women aged 30 years and older. In younger women, cytology has a better performance, since the high prevalence of hr HPV infection makes the specificity of HPV-testing even worse. In vaccinated cohorts hr HV-testing is preferred, since lesions are thought to be smaller and more easily missed by cytology. In low resources setting, hr HPV-testing significantly reduces cervical cancer incidence and cancer mortality, in comparison with cytology and visual inspection based screening.

Disclaimer: No potential conflict of interest.
Citation: *European Medical Journal - Gynecology and Obstetrics,* 2012:1:34-38

Introduction

Cervical cancer is the third most common cancer in women worldwide.(1) Cervical cancer and pre-cancer arise at the transformation zone where the squamous and the columnar epithelium of the endocervix meet. HPV infection at this site is the primary step in the pathogenesis of this disease. HPV infection induces changes in the cell cycle, by changing methylation of cell DNA, inducing transcription of viral oncogens and thereby formation of proliferation proteins.(2)

HPV infection is common as 80% of all women are infected at some point in their lives,(3) but most of these infections are transient. HPV infections occur most in young women after initial sexual contact. Less than 3-5% of woman infected with a high risk HPV type acquire cervical cancer.(4)

Screening used to focus on the detection of precancerous or early invasive lesions by cytology. New screening methods arise, since more about the pathogenesis is known.

The first screening test was based on the cytological detection of abnormal cells in a smear that was taken at the cervical transformation zone. This test was invented by and named after Georgios Papanikolaou in the beginning of last century, and therefore was called PAP-smear. Screening by cytology was

introduced for screening programs in Northern America and Europe 50 years ago. Organised screening programs are responsible for an important reduction in the incidence of cervical cancer in some parts of the developed world.[5]

Liquid based monolayer cytology has replaced the conventional PAP-smear in large parts of the world. In the last decade, automated computer image analysis systems for screening by cytology have been introduced. Unfortunately these systems are expensive and still need some human supervision. Therefore cytology screening is not available in low resource countries.

Cytology based screening still is the most commonly used primary screening test, despite some important disadvantages. It has a low sensitivity to find precancerous lesions ranging from 38%-87% and specificity ranging from 86%-98%,[6-8] leaving a part of the cervical cancer precursors undiagnosed. A short screening interval is therefore necessary. Sensitivity and specificity depend on cut-off values of cytology. When the cut-off for cytology is low (ASCUS: Atypical Squamous Cells of Unknown Significance), sensitivity improves at the cost of lower specificity.

Hr HPV-testing as triage after equivocal PAP-smear

ASCUS is associated with a risk for CIN 2+ (CIN 2, CIN 3, adenocarcinoma in situ) of 9.7% (95% Confidence Interval: 7.7-11.7%), and a very low risk for cervical cancer (0.1-0.2%). Hr HPV-testing as a triage test in ASCUS-cytology showed a high sensitivity in predicting high grade CIN (92.5% (95% CI: 90.1-94.9%).[9] It is at least as sensitive as an immediate colposcopy.[10]

Hr HPV-testing in secondary screening after treatment

Despite treatment for CIN, the risk of (recurrent) disease after treatment is higher than in the general population. A continued surveillance and follow up is required. Hr HPV persistency is recorded in 20% of these cases and it is strongly correlated with residual/recurrent CIN.[10,11]

The best way to monitor this high risk population is a combined cytology and HPV test at six months (sensitivity of 96% (95% CI 89-99), specificity 81% (95% CI 77-84)). A single hr HPV-test is also highly sensitive (OR: 1.27 (95%CI 1.06-1.51), with only a slight loss in specificity (OR: 0.94 (95%CI 0.87-1.01)). In women with a negative co-test (cytology+hr HPV DNA), testing at 12 months after treatment can safely be skipped, but should be repeated at 24 months.[10]

HPV testing in primary screening

Since HPV infection is a necessary step in the pathogenesis of cervical cancer and pre-cancer, methods based on the detection of high risk HPV DNA can identify women at risk for cervical cancer.

Several HPV DNA tests are available. Hybrid Capture 2 (HC2) was developed in 1997. This test recognizes thirteen high-risk HPV genotypes, but the test cannot determine the specific HPV genotype present. It is the most frequently used diagnostic HPV test worldwide. HC2 is FDA approved for ASCUS triage and for primary screening in conjunction with cytology in women over age 30.[12] The sensitivity is 23% higher than that of cytology, the specificity is -7% lower in comparison to cytology based screening.[9] The pooled specificity of HC2 in excluding high-grade cervical pre cancer is 88.2% (95% CI: 86.2-90.1%).[4]

For detecting a specific hr HPV genotype, real time PCR HPV testing was introduced. Using that test in primary screening resulted in a pooled sensitivity that was lower than HC2 84.2% (95% CI 77-91.5%), but the pooled specificity was higher 95.1%, (95% CI: 93.4%- 96.8%).[4]

Primary screening with HPV DNA testing results in a higher sensitivity, but lower specificity in detecting high grade CIN in comparison to cytology based screening. A higher sensitivity gives a higher negative predictive value and screening intervals can be extended. Screening intervals of at least 6 years are as safe as a screening interval of 3 years with cytology.[13]

Furthermore HPV testing is more effective in detecting adenocarcinoma and its precursors than cytology.[14]

A lower specificity could be the result of the detection of transient infections that do not cause cytologic changes.[15] This is the main reason not to use HPV DNA testing in primary screening since more women are referred to colposcopy[16] leading to a greater cost and psychological burden for these women.

Transient HPV infections are more common in women aged 30 and younger. So primary HPV-screening in this category is not cost-effective. Ronco *et al* stated that HPV screening leads to overdiagnosis of regressive CIN 2 in women aged 35 years and younger.[17] Rijkaart *et al*, found that HPV testing in women aged 29-33 years does not result in an overdiagnosis of regressive CIN and HPV based screening can be implemented in screening programs starting at the age of 30 years.[18]

The data of Ronco *et al* support the use of stand-alone hr HPV-testing as the primary screening test and HPV-positive women older than 35 should be triaged with cytology or molecular markers such as P16 before referral to colposcopy.

Combined cytological and HPV screening is thought not to be cost-effective, since there is a greater cost, without significantly increasing sensitivity.[17] HPV as an initial test triaged with cytology could be cost effective since it can extend screening intervals based on longer-term protection from HPV negative tests.[19]

The management of HPV positive women is still unclear. Different triage algorithms are described.[20]

Primary HPV testing with triage cytology

HPV DNA testing provides an automated, objective and very sensitive primary test. Cytology can be reserved for the 5-15% of women who are hr HPV positive. HPV-based screening of women older than 30 years followed by cytology triage of hr HPV positive women, does not increases diagnostic work-up and over-treatment and therefore appears to be the most feasible cervical screening strategy.[21,22]

Triage with HPV typing information

HPV type 16 is more persistent and more often associated with high grade disease. HPV 18 is more often associated with cytology negative endocervical or glandular lesions, that remain hidden for colposcopy.[4] These two HPV genotypes account for 70% of the cervical cancers. Khan et al suggested a less aggressive management of HC2 positive, but HPV 16 and 18 negative women, since only 3% of these infections lead to high grade CIN in the next 10 years, whereas for HPV 16 positive women a cumulative incidence rate of 17.2% and for HPV 18 13.6% was seen.[23] HPV 16/18 positive and cytology-negative; women should be referred to colposcopy, since there is a short-term risk for CIN3.[24]

Triage with p16 INK4A (9)

P16 is a cycline dependent kinase inhibitor which is downregulated by the retinoblastoma (RB) gene, it is overexpressed in cervical cancer cell lines where RB is inactivated by HPV E7 oncoproteins. It is therefore a marker for activated expression of viral oncogenes.

HPV testing (HC2) with p16 INK4A triage has a sensitivity of 88% (95% CI: 80-94) and specificity of 61% (95% CI: 57-64%). The sensitivity is much higher than cytology. The specificity is comparable with cytology, therefore an equal number of women are referred to colposcopy. In women with CIN, the proportion of women that shows p16 overexpression, ranges from 53% in CIN 1 to 91% in CIN 3 or invasive cancer.[25] Part of the p16 positive lesions regress, especially when the percentage of cells overexpressing p16 is low.

Methylation markers

Promoter methylation of tumor suppressor genes has been reported to be an early event in carcinogenesis. Various methylated gen promoters for cervical neoplasia have been tested, but there are no large population based studies. Eijsink *et al* identified a set of new methylation markers with a higher identification of CIN3 and cervical cancer and higher percentage of correct referrals for colposcopy compared to hr HPV-testing in combination with conventional cytology.[26]

HPV load slope curves

Depuydt *et al* discovered a new strategy to differentiate between transient and persistent infection. The profile of viral load evolution over time could distinguish HPV infections with carcinogenic potential form infections that regress.[27] Transient infections generated similar increasing and decreasing slope curves. In persistent infections, the viral load slope was less steep but linear. In this study only single type infections were analyzed, suggesting that combining viral load at two time points could identify women that have a persistent infection and therefore are at risk of developing precancerous and invasive lesions.

Screening in a HPV vaccinated cohort

In a vaccinated cohort, the risk of cervical cancer and pre-cancer is significantly reduced by preventing HPV16 and 18 infection. The lesions are expected to be smaller with a higher risk of missing these by cytology or colposcopy directed biopsies. Therefore HPV typing is thought to be a better primary screening test in a vaccinated population. It is thought that in this population the start of screening could be delayed and screening intervals could be longer.[24]

Lower resources settings

In developing countries, a cost effective program with immediate treatment of screening positive women is the most important goal. HPV testing based on fast-HPV technology with immediate cervical cryotherapy of HPV positive women would be a practical approach.

Sankaranarayanan *et al* performed a study in rural India, where the effect of a single round of screening with HPV-test, cytology and a visual inspection test was compared. HPV-test was the only test that was related to a significant reduction in the numbers of advanced cervical cancers and cancer deaths.[28]

Conclusion

In unvaccinated women under the age of 30, current evidence supports primary screening starting at 25 years with cytology and hr HPV-DNA testing in cases of equivocal cytology.[24] In women above the age of 30, primary screening with hr HPV-DNA testing with cytology triage is currently the most feasible option. For the moment cytology screening intervals are kept relatively short (3 years). As follow-up trials are published, HPV screening intervals could be extended to 6 years for HPV-negative women without loss of sensitivity.

In vaccinated women, screening should start at age 25 years and HR-HPV-DNA testing with cytology triage every 5 years is currently recommended.

In the future, other triage tests for HPV positive women will become available, giving an even better prediction of persistent HPV infection and progressive CIN. These triage tests are at the moment available but they are not validated in clinical settings in large population based trials. Furthermore, the organisation of cervical cancer screening in large populations remains the mainstay of cost-effective cancer prevention.

References

1. **Arbyn M, Castellsagué X, de Sanjosé S et al**, *"Worldwide burden of cervical cancer in 2008", Ann. Oncol. (2011), 12: pp. 2675-86.*

2. **Munoz N, Castellsagué X, Berrington de Gozalez A et al**, *"HPV in the etiology of human cancer", Vaccine (2006), S3: pp. 1-10*

3. **Ault K A**, *"Epidemiology and natural history of human papillomavirus infections in the female genital tract", Infect. Dis. Obstet. Gynecol. (2006), pp.1-5.*

4. **Cuzick J, Arbyn M, Sankaranarayanan R et al**, *"Overview of Human Papillomavirus-based and other novel options for cervical cancer screening in developed and developing countries", Vaccine (2008), 26S: pp. 29-41.*

5. **Arbyn M, Raifu A O, Weiderpass E et al**, *"Trends of Cervical cancer mortality in the member states of the European Union", Eur J Cancer. (2009), 45: pp. 2640-8.*

6. **Whitlock E P, Vesco K K, Eder M et al**, *"Liquid-based cytology and human papillomavirus testing to screen for cervical cancer: a Systematic Review for the U.S. preventive services task force", Ann. Intern. Med. (2011), 155, 10: pp. 687-698.*

7. **Sykes P H, Harker D Y, Miller A et al**, *"A randomized comparison of SurePath liquid-based cytology and conventional smear cytology in a colposcopy clinic setting", BJOG (2008), 115: pp. 1375-1381.*

8. **Boone J, Erickson B, Huh W**, *"New insights into cervical cancer screening", J. Gynecol Oncol. (2012), 23, 4: pp. 282-287.*

9. **Arbyn M, Saieni P, Meijer C et al**, *"Clinical applications of HPV testing: a summary of meta-analyses", Vaccine (2006), S3: pp. 78-89.*

10. **Origoni M, Cristoforoni P, Costa S et al**, *"HPV-DNA testing for cervical cancer precursors: from evidence to clinical practice", Ecancer (2012), 6, 258: pp1-15.*

11. **Arbyn M, Paraskevaidis E, Martin-Hirsch P et al**, *"Clinical Utility of HPV-DNA Detection: Triage of minor cervical Lesions, Follow-up of Women treated for high-grade CIN: an Update of pooled Evidence", Gynecol. Oncol. (2005), 99: pp. 7-11.*

12. **Zhao C, Yang H**,*"Approved Assays for detecting HPV-DNA-Design, Indications and VAlidation, Cytopathology and More", Website of the College of American Pathologists (2012).*

13. **Dillner J, Rebolj M, Birembaut P et al**, *"Long term predictive Values of Cytology and Human Papillomavirustesting in Cervical Cancer Screening: joint European Cohort Study", BMJ (2008), 25: pp. 3044-3050.*

14. **Castle P E, Glass A G, Rush B B et al**, *"Clinical Human Papillomavirus Detection Forcasts Cervical Cancer Risk in Women over 18 Years of Follow up", J. Clin. Oncol.(2012), 30, 25: pp. 3044-3050.*

15. **Naucler et al**, *"Human Papillomavirus and Papanicolaou Test to Screen for Cervical Cancer", N. Engl. J. Med. (2007) 367, 16: pp. 1589-1597.*

16. **Mayrand M-H, Duarte-Franco E, Coutlée F et al**, *"Randomized Controlled Trial of Human Papillomavirus Testing versus Pap Cytology in the Primary Screening for Cervical Cancer Precursors: Design, Methods and Preliminiary Accrual Results of the Canadian Cervical Cancer Screening Trial (CCCAST)", Int. J. Cancer (2006), 199: pp. 615-623.*

17. **Ronco G, Giorgi-Rossi P, Carozzi F et al**, *"Efficacy of Human Papillomavirus Testing for the Detection of Invasive Cervical Cancers and Cervical Intra-Epithelial neoplasia: A Randomized Controlled Trial", Lancet Oncol. (2010), 11: pp. 249-57.*

18. **Rijkaart D, Berkhof J, Rozendaal L et al**, *"Human Papillomavirus Testing for the Detection of High-grade Cervical Intra-epithelial Neoplasia and Cancer: Final Results of the POBASCAM Randomised Controlled Trial", Lancet Oncol. (2012), 13: pp. 78-88.*

19. **Cuzick J, Szarewski A, Mesher D et al**, *"Long-Term Follow-up of Cervical Abnormalities among Women screened by HPV testing and cytology: results of the Hammersmith study", Int. J. Cancer (2008), 122: pp. 2249-300.*

20. **Arbyn M, de Sanjosé S, Saraiya M et al**, *"EUROGIN 2011 roadmap on prevention and treatment of HPV-related disease", Int. J. Cancer (2012), 131, 9: pp. 1969-82.*

21. **Naucler P, Ryd W, Törnberg S et al,** *"Efficacy of HPV DNA Testing With Cytology Triage and/or Repeat HPV DNA Testing in Primary Cervical Cancer Screening", J. Natl. Cancer Inst.(2009), 101: pp. 88-99.*

22. **de Kok I M, van Rosmalen J, Dillner J et al**, *"Primary Screening for Human Papillomavirus compared with Cytology Screening for Cervical Cancer in European Settings: Cost Effectiveness Analysis based on a Dutch Microsimulation Model", BMJ (2012), 344, e670: pp. 1-14.*

23. **Khan M J, Castle P E, Lorincz A T et al**, *"The Elevated 10-years Risk of Cervical Precancer and Cancer in Women With Human Papillomavrius Type 16 or 18 and the possible utility of Type-specific HPVtesting in Clinical Practice", J. Natl. Cancer Inst. (2005), 97, 14: pp. 1072-1079.*

24. **Saslow D, Solomon D, Lawson H W et al**, *"American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Screening Guidelines for the prevention and Early Detection of Cervical Cancer", Am. J. Clin. Pathol. (2012) 62, 3: pp. 147-171.*

25. **Carozzi F, Confortini M, Dalla Palma P et al**, *"Use of p16-INK4A overexpression to increase the specificity of human papillomavirus testing: a nested substudy of the NTCC randomized controlled trial", Lancet Oncol. (2008), 9: pp. 937-945.*

26. **Eijsink J J, Lendvai A, Deregowski V et al**, *"Methylation marker panel as triage test in high-risk human papillomavirus positive patients", Int. J. Cancer (2012), 130: pp. 1861-1869.*

27. **Depuydt C E, Criel A M, Benoy I H et a**l, *"Changes in type-specific human papillomavirus load predict progression to cervical cancer", J. Cell. Mol. Med. (2012), 20, 10: pp. 1-9.*

28. **Sankaranarayanan R, Nene B M, Shastri S S et al**, *"HPV Screening for Cervical Cancer in Rural India" N. Engl. J. Med. (2009), 360, 14: pp. 1385-1394.*

Risk of Ovarian Malignancy (ROMA™) - Determining the Likelihood of Malignancy in Women with Pelvic Mass

Zivjena Vucetic

Director, Global Scientific Affairs at Fujirebio Diagnostics, Inc.

Zivjena Vucetic, PhD

Abstract

Ovarian cancer is a malignancy with poor prognosis and is still the leading cause of death from gynecological malignancies worldwide. A contributing factor to this has been the lack of reliable diagnostic tools for the detection of ovarian cancer. This review focuses on new bloods tests, HE4 and Risk of Malignancy Algorithm (ROMA) that have recently been introduced for risk assessment and management of ovarian cancer patients. Early detection, treatment and management of disease by specialized gynecologic oncologists and new therapeutic advances hold promise for improved outcomes in ovarian cancer patients.

Disclaimer: No potential conflict of interest
Citation: *European Medical Journal - Gynecology and Obstetrics*, 2012:1:40-43

Introduction

Ovarian cancer is the leading cause of death from gynecologic malignancies in the United States with annual incidence of 22,000 cases. Estimated annual mortality rate is approximately 15,460[1] cases. Ovarian cancer has a good prognosis if detected in its early stages and if treated by specialized gynecologic oncology surgeons,[2] however more than three-quarters of cases are diagnosed in the advanced stage and are associated with poor survival rates of 10-30%.[3] These poor outcomes reflect the lack of effective tools for early detection of ovarian cancer and the limitations of current treatment options for ovarian cancer, which generally include cytoreductive surgery followed by adjuvant chemotherapy.

Recent studies have shown that women with ovarian cancer develop non-specific symptoms, including pelvic or abdominal pain, increased abdominal size, bloating, urinary urgency and difficulty eating or feeling full quickly, months before diagnosis.[4] However, ovarian cancer is commonly discovered on surgery for an adnexal mass. It is estimated that 5–10% of women at some point in their lives will undergo surgical evaluation of an adnexal mass and up to one fifth of surgically removed masses will have a diagnosis of ovarian cancer . In the premenopausal women, the risk of a mass being malignant is 7-13%, while in the postmenopausal women it is 30-40%.[6] Thus, the presence of symptoms and the findings of an adnexal mass increase the risk of malignancy and should prompt thorough diagnostic evaluation.

The primary goals of diagnostic evaluation of women who present with adnexal masses are to confirm that adnexal mass is of ovarian origin and to differentiate whether it is benign or malignant. In order to determine the most appropriate management strategy that would ensure the optimal outcome for the woman with adnexal mass it is essential to effectively triage the risk for malignancy. Combination of multiple diagnostic modalities improves the physician's ability to preoperatively assess women with adnexal mass. Diagnostic techniques that are commonly used are: clinical exam and thorough medical history, imaging (e.g. transvaginal ultrasound) and serum tumor maker (e.g. CA125) measurements. According to a study by the Agency for Healthcare Research and Quality, which assessed

diagnostic strategies for distinguishing benign from malignant masses, all current diagnostic modalities showed significant trade-offs between sensitivity and specificity.[7] Although serum CA125 test does not have FDA-cleared indication as preoperative diagnostic aid in women with ovarian masses that are suspected to be malignant, CA125 is commonly used and recommended by the American Congress of Obstetricians and Gynecologists (ACOG) and the Society of Gynecologic Oncologists (SGO) for this indication.[8,9] The main clinical disadvantage of CA125 for adnexal mass assessment is its insufficient sensitivity for detecting early stage cancer and decreased specificity, due to false elevations in benign obstetric-gynecologic conditions such as endometriosis, leiomyomas, pelvic inflammatory disease and pregnancy.[10]

HE4 – ovarian cancer specific biomarker

HE4 (Human epididymis protein 4) is a member of a family of four disulphide core (WFDC) domain proteins and the function of this protein is unknown.[11] The HE4 gene is elevated in serum from women with ovarian cancer and its expression in normal tissues, including ovary, is low.[12] Several studies have indicated that using HE4 alone or in combination with CA125 may improve the accuracy for detection of ovarian cancer. In a study by Moore et al. that evaluated nine known biomarkers for ovarian cancer, HE4 showed the highest sensitivity at a set specificity for the detection of ovarian cancer, particularly in early stage disease.[13] In this study, the combination of HE4 and CA125 was a more accurate predictor of malignancy than either marker alone, with a sensitivity of 76% and a specificity of 95%. Additional studies confirmed that measuring serum HE4 concentrations along with CA125 concentrations may provide higher accuracy for detecting ovarian cancer, and may improve the accuracy for detection of ovarian cancer at an earlier stage.

Additionally, a number of studies demonstrated improved specificity of HE4 for discriminating ovarian cancers from benign gynecologic disease. Huhtinen et al. was first to report that serum concentration of HE4 was significantly higher in patients with endometrial and ovarian cancer than in patients with ovarian endometriomas or other types of endometriosis.[14] These results were later confirmed in studies reported by Montagnana et al [15] and Holcomb et al.[16] Recently, in a large study of 1042 pre- and postmenopausal women with benign gynecological disorders HE4 was found to be less frequently elevated than CA125 in several benign diseases.[17] For example, HE4 was elevated in only 3% of premenopausal women with endometriosis, while in the same group CA125 was elevated in 72% of women. Unlike CA125 which can be elevated in one fourth of pregnant women and a third of patients with pelvic inflammatory diseases (PID), HE4 is not elevated in pregnancy and PID. [16,18] In addition, in healthy premenopausal women HE4 does not appear to oscillate during menstrual cycle.[19]

ROMA™ test is an aid in determining the likelihood of malignancy in women who present with an adnexal mass

In September 2011, the ROMA test received clearance from the FDA as an aid in assessing whether a premenopausal or postmenopausal woman who presents with an adnexal mass is at high or low likelihood of having a malignancy. ROMA is a qualitative serum test that combines the results of 2 biomarkers - HE4, CA125 and menopausal status into a single score and is indicated for women who meet the following criteria: over age 18 and adnexal mass present for which surgery is planned.

The effectiveness of ROMA to aid in estimating the risk of malignancy was determined in a prospective, multi centre, blinded clinical trial of 461 women over 18 years (240 pre- and 221 post-menopausal) presenting with an adnexal mass that requires surgical intervention.[20] For each patient, an initial cancer risk assessment (ICRA) was completed by a non-gynecological oncologist, providing the generalist's assessment of the patient's mass as benign (negative) or malignant (positive) based upon the information available to the generalist during their work-up of the patient. The corresponding histopathology reports were collected and the stratification into low and a high risk groups for finding malignancy on surgery was determined using ROMA. The incidence of ovarian cancers was 10%. ROMA achieved 100% sensitivity at 74.5% specificity, a positive predictive value (PPV) of 13.8% and a negative predictive value (NPV) of 100% for stratification of premenopausal women with epithelial ovarian cancer into low likelihood and high likelihood groups of having malignancy. In postmenopausal women, ROMA had 92.3% sensitivity at 76.8% specificity, a PPV of 50.0% and NPV of 97.5% for stratification into low

and high likelihood groups of having malignancy. When considering all women together ROMA had a sensitivity of 93.8%, a specificity of 74.9% and a NPV of 99.0%.

In a separate prospective, multi centre trial conducted at 12 US tertiary care institutions, 566 women undergoing surgery for adnexal mass were classified using ROMA into high and low likelihood groups for having epithelial ovarian cancer.[21] The incidence of ovarian cancers in this cohort was 23%. In the postmenopausal group at specificity of 75.0%, ROMA had sensitivity of 92.3%. In the premenopausal group at the specificity of 74.8% ROMA provided a sensitivity of 76.5% for classifying into high likelihood and low likelihood groups for having malignancy.

Additionally, seven distinct, single centre, multinational studies were published that validated the use of ROMA for adnexal mass risk stratification.[22-28] Combined, these studies assessed over 4,000 women with adnexal mass that were scheduled to undergo surgery in the United States, Europe and Asia. The range of sensitivity for ROMA test was from 75% – 94%, at specificity from 75% - 95%. ROMA demonstrated consistent and reliable performance for classifying women with adnexal mass into high risk and low likelihood groups for epithelial ovarian cancer.

Conclusions

In the US, women with adnexal masses present primarily to gynecologists, primary care physicians or general surgeons for initial diagnostic evaluation. According to a Practice Bulletin from the American Congress of Obstetrics and Gynecology (ACOG) an important dilemma is faced by these physicians as to which patients are appropriate for referral to a gynecologic oncologist, and/or to an institution experienced in gynecologic cancer surgery. Several recent studies have demonstrated that ovarian cancer patients managed by gynecologic oncologists and at high volume institutions are more likely to undergo complete surgical staging, and optimal cytoreductive surgery with fewer complications and better survival rates than patients treated by surgeons less familiar with the management of ovarian cancer. Based on the available clinical evidence, ROMA test represents an important tool for improved triage of women diagnosed with an adnexal mass which can ultimately lead to improved patient outcomes.

References

1. ***Jemal A, et al***. *Cancer statistics, 2010. CA Cancer J Clin, 2010. 60(5): p. 277-300.*

2. ***Giede KC et al***. *Who should operate on patients with ovarian cancer? An evidence-based review. Gynecol Oncol. 2005 Nov;99(2):447-61.*

3. ***Source***: *1999-2006 National Cancer Institute –Surveillance Epidemiology and End Results (NCI-SEER)*

4. ***Goff BA et al***. *Development of an ovarian cancer symptom index: possibilities for earlier detection. Cancer 2007;109:221-27.*

5. ***Trimble EL***.*The NIH Consensus Conference on Ovarian Cancer: screening, treatment, and follow-up.Gynecol Oncol. 1994 ;55(3 Pt 2):S1-3.*

6. ***B.Y.K. Ronald S. Gibbs, Arthur F. Haney, Ingrid Nygaard***, *eds.Danforth's Obstetrics and Gynecology. 2008: Lippincott Williams & Wilkins.*

7. ***Myers ER et al***. *Evid Rep Technol Assess (Full Rep). Management of adnexal mass.2006 Feb;(130):1-145.*

8. ***ACOG*** *Practice Bulletin. Clinical Management Guideline for Obstetrician-Gynecologists. Management of Adnexal Masses. Obstet Gynecol. 2007;110:201-213.*

9. ***The Society of Gynecologic Oncologists.*** *Guidelines for referral to a gynecologic oncologist: rationale and benefits. Gynecol Oncol. 2000 Sep;78(3 Pt 2):S1-13*

10. ***Jacobs I, Bast RC Jr***. *The CA 125 tumour-associated antigen: a review of the literature.Hum Reprod. 1989 Jan;4(1):1-12*

11. ***Bouchard D et al***. *Proteins with whey-acidic-protein motifs and cancer. Lancet Oncol 2006;7:167-74.*

12. ***Drapkin R et al***. *Human epididymis protein 4 (HE4) is a secreted glycoprotein that is over-expressed by serous and endometrioid ovarian carcinomas. Cancer Res 2006;65:2162-69.*

13. ***Moore RG et al***. *The use of multiple novel tumor biomarkers for the detection of ovarian carcinoma in patients with a pelvic mass. Gynecologic Oncol 2008;108:402-408.*

14. ***Hutinen, K, et al***. *Serum HE4 concentration differentiates malignant ovarian tumours from benign endometriotic cysts. Br J Cancer. 2009:100;1315-1319.*

15. ***Montagnana M, et al***.*Usefulness of serum HE4 in endometriotic cysts.Br J Cancer. 2009 Aug 4;101(3):548.*

16. ***Holcomb K, et al***. *Human epididymis protein 4 offers superior specificity in the differentiation of benign and malignant adnexal masses in premenopausal women. Am J Obstet Gynecol. Am J Obstet Gynecol. 2011;205(4):358.e1-6.*

17. ***Moore RG, et al***. *Serum HE4 levels are less frequently elevated than CA125 in women with benign gynecologic disorders. Am J Obstet Gynecol. 2012 Apr;206(4):351.e1-8.*

18. ***Moore RG, et al***. *Serum levels of the ovarian cancer biomarker HE4 are decreased in pregnancy and increase with age.Am J Obstet Gynecol. 2012 Apr;206(4):349.e1-7.*

19. ***Hallamaa M, et al***. *Serum HE4 concentration is not dependent on menstrual cycle or hormonal treatment among endometriosis patients and healthy premenopausal women.Gynecol Oncol. 2012 Mar 14. [Epub ahead of print]*

20. ***Moore RG, et al***. *Evaluation of the Diagnostic Accuracy of the Risk of Ovarian Malignancy Algorithm in Women With a Pelvic Mass. Obstet Gynecol. 2011;118(2, Part 1):280-288.*

21. ***Moore RG, et al***. *A novel multiple marker bioassay utilizing HE4 and CA125 for the prediction of ovarian cancer in patients with a pelvic mass. Gynecol Oncol. 2009 ;112(1):40-6.*

22. **Van Gorp T, et al**. *HE4 and CA125 as a diagnostic test in ovarian cancer: prospective validation of the Risk of Ovarian Malignancy Algorithm. Br J Cancer. 2011;104(5):863-870.*

23. **Jacob F, et al**. *No benefit from combining HE4 and CA125 as ovarian tumor markers in a clinical setting. Gynecol Oncol. 2011;121(3):487-491.*

24. **Lenhard M, et al**. *The diagnostic accuracy of two human epididymis protein 4 (HE4) testing systems in combination with CA125 in the differential diagnosis of ovarian masses. Clin Chem Lab Med. 2011 Sep 16. [Epub ahead of print]*

25. **Molina, R, et al**. *HE4 a novel tumor marker for ovarian cancer: comparison with CA 125 and ROMA algorithm in patients with gynecological diseases. Tumour Biol. 2011 Dec;32(6):1087-95.*

26. **Montagnana M, et al**. *The ROMA (Risk of Ovarian Malignancy Algorithm) for estimating the risk of epithelial ovarian cancer in women presenting with pelvic mass: is it really useful? Clin Chem Lab Med. 2011;49(3):521-525.*

27. **Ruggeri G, et al**. *HE4 and epithelial ovarian cancer: comparison and clinical evaluation of two immunoassays and a combination algorithm. Clin Chim Acta. 2011;412(15-16):1447-1453.*

28. **Kim YM, et al**. *Evaluation of the accuracy of serum human epididymis protein 4 in combination with CA125 for detecting ovarian cancer: a prospective case-control study in a Korean population. Clin Chem Lab Med. 2011;49(3):527-534.*

Vaginal pH Self-Screening as a KISS Regimen in Prevention of Early Preterm Birth

Udo B. Hoyme

Chief Physician, HELIOS Klinikum Erfurt, Germany

Univ.-Prof.Dr.med.habil. Prof.Dr.h.c. Udo B. Hoyme

Abstract

Self-measurement of vaginal pH is an established screening procedure for prevention of premature birth due to abnormal vaginal flora and bacterial vaginosis. In the Erfurt and Thuringia studies women were instructed to see their physician immediately if their vaginal pH was abnormal (> 4.5) or other risk factors were present, so results could be confirmed and therapy started. Treatment was with Lactobacillus acidophilus or, for bacterial vaginosis, antibiotics. In the initial trial, 0.3 % of the neonates with a gestational age < 32 + 0 weeks were seen in an intervention group versus 3.3 % ($p < 0.01$) in the control group; in the larger Thuringia study, the figures were 0.94 versus 1.36 % ($p < 0.01$). The rate of newborns < 1.000 g was significantly reduced to 0.38 %, the lowest incidence ever seen in Germany. After discontinuation of the Thuringia trial in 2000, the pre-term birth rates returned to the levels prior to the programme, however, the innovative pH measurement regime described has been introduced in > 20 countries so far.

Disclaimer: Potential conflict of interest: pH-EcoCare was designed and marketed in cooperation with the author.
Citation: *European Medical Journal - Gynecology and Obstetrics*, 2012:1:44-47

Introduction

Abnormal vaginal flora (AVF) as well as bacterial vaginosis (BV) have a significant relative risk for miscarriage or preterm birth. Furthermore, bacterial infectious agents play an important role, also in the etiology of ectopic pregnancy, spontaneous abortion, stillbirth, congenital and perinatal infections and puerperal maternal infections. Since Chlamydia trachomatis, Neisseria gonorrhoeae and BV have been associated with an increased risk of febrile morbidity especially after surgical abortion, routine screening appears to be indicated prior to the procedure in most populations, but is also considered in general for pregnancy.[1-3]

Despite all interventional efforts preterm birth rates have remained unchanged for years at about 6 – 8 % throughout Germany. In contrast, both perinatal morbidity and mortality have been reduced significantly over the last years. With the current high standard of neonatal medicine, a further improvement of those results can only be expected if we succeed in reducing prematurity as the main contributor to perinatal morbidity and mortality.[1, 3] Because of the preventive character of all measures this requires not only a medical but also a socio-political effort.

AVF and BV, an anaerobic dysbiosis, are found in up to 20 % of pregnancies and represent a relative risk for miscarriage and prematurity of 1.4 – 6.9.[1, 4-7] An adequate treatment regime, especially in the early stages of pregnancy, can lead to a significant reduction of prematurity.[6-8] The efficacy of this concept, in which the pregnant women actively take part, has been investigated in the Erfurt and Thuringia trials.[3, 11]

Patients and Methods

The objective of these trials was to prove the efficacy of vaginal pH screening as a substitute tool for AVF and BV during pregnancy. Intravaginal pH self-

Table 1. Data from the Thuringia Prematurity Prevention Campaign 1998: delivery (controlled for gestational age) at the Department of Obstetrics, Erfurt. (n = 2,722)

Delivery (gestational age)	Participants (pH self measurement)	Controls A (pH measured by physician)	Controls B (no measurement)
	n = 381	n = 1,001	n = 1,340
≥ 37 + 0	91.9%	90.7%	85.4%
32 + 0 / 36 + 6	7.9%	7.1%	10.4%
< 32 + 0	0.3%	2.2%	4.1%

measurements were carried out twice weekly by the women, as the obstetrician´s examinations at 4-week intervals, were not considered to be sufficient. In this study, involving more than 200 local obstetricians, it was impossible and also not intended to investigate specifically the impact of AVF or BV on prematurity, neither to collect new epidemiological data, nor to reassess diagnostic measures and compare different treatment regimes. The aim was rather to estimate the impact on self-measurement of vaginal pH as a sign of a high risk of preterm delivery.[3]

Each patient was asked to consult her gynecologist immediately when risk indicators or symptoms relevant for prematurity occurred, especially when a pH value of or above 4.6 was obtained. The gynecologist had to decide if the elevated pH was attributable to 1. a physiological condition, 2. pH elevation without evident infection or pathogen present (possibly AVF without BV), 3. BV according to the Amsel criteria, or 4. an indication for hospital admission, e. g. rupture of the membranes or uterine bleeding.

At the obstetrician´s discretion, the patient was assigned to receive either no therapy, a 6- or 12-day course of intravaginal probiotic therapy (Gynoflor®, Nourypharma, Oberschleissheim, Germany), 5 days of vaginal clindamycin cream (Sobelin-Creme®, Pharmacia & Upjohn, Erlangen, Germany) or admission to the hospital for specific treatment according to the diagnosis.

Results

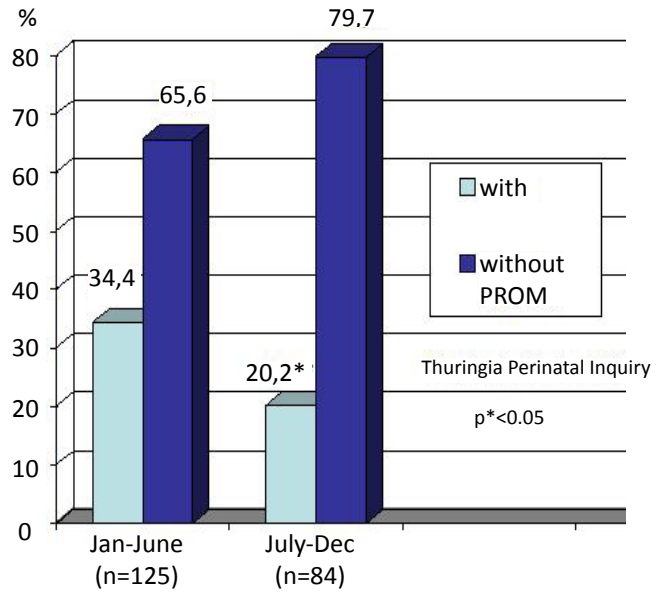
In December 1998, 381 women of a total of 2,722 delivering women in that period in Erfurt maternity were included in the pilot trial (14 %). The 2,341 women not participating in the trial served as a control group. Preterm birth rate before the end of 32 gestational weeks was only 0.3 % among the study patients, compared with 2.2 % of patients seen every 4 weeks by physicians, being informed about the trial, but not involved in self-sampling and 4.1 % in a group of pregnant women who received only conventional prenatal care (Table 1). The majority of women appreciated the privacy and preferred the self-care, rather than the feeling of an “object” being looked after, a clear paradigm shift.

Also the evaluation of the perinatal data of 16,276 deliveries during the year 2000 in Thuringia showed similar trends: the total number of preterm births before the end of 32 weeks was significantly less in the 6-month period of self-test compared to the previous 6 months without self-test, also in the different birthweight groups (Table 2). Women doing self-sampling during the study period and reporting back (607 self-sampling women of 8,406 in total, 8 %) had a reduced risk of preterm birth at < 32 + 0 weeks (0.3 vs. 1.58 %; $p < 0.05$) and at < 37 + 0 weeks (5.3 vs. 8.5 %; $p < 0.01$) versus controls (first 6 months of year 2000, n = 7,870). Similar results were obtained when comparing the birth weights < 2,500 g (3.45 vs. 6.92 %; $p < 0.001$). Moreover, more than 1/3 of early premature births were connected with early rupture of membranes in the 1st half of the year; this was only the case in 1/5 in the 2nd half (Fig.1).

Discussion

Abnormal vaginal flora and bacterial vaginosis is a known risk factor for preterm birth. The VIP trial in which enrolment was after 20 weeks of pregnancy found a relative rate of preterm birth of 1.6 for women with BV, comparable for the risk of harbouring C. trachomatis or trichomoniasis.[4] Aerobic types of colpitis with an increase of the pH value[6-8] as well as intra- and extra-amniotic infections with enteropharyngeal pathogens are also demonstrated to contribute towards prematurity.[9]

Figure 1. Thuringia Prematurity Prevention Campaign 2000: Share of Premature Rupture of Membranes for Early Preterm Birth (< 32 + 0 weeks)



Dennemark et al.[10] were able to show that by early intervention either with lactobacillus preparations or with intravaginal Clindamycin treatment, a distinct reduction of prematurity could be obtained. In principle, lactobacillus preparations cannot yet be considered a scientifically proven causal therapy in women with an abnormal vaginal flora in pregnancy, but the main objective of treatment in both the Dennemark and the Erfurt/Thuringia investigations was the prolongation of pregnancy.

The Erfurt and Thuringia programmes represent a prospective observational study. The main benefit is that because of the active involvement of the pregnant women pH changes could be recognized early in pregnancy and as a consequence most abnormalities relevant for late miscarriage or premature birth could be addressed with an immediate therapy. The results confirm the positive consequences of the applied measures.

However, the study also has disadvantages.[11] Firstly, it is not known what the pathophysiological correlate of an increased pH is. Other signs of imminent preterm birth may be involved in women with increased pH: cervicitis, frequent and recent sexual contact, uterine bleeding, etc. Secondly, we have no detailed information of the medication and actions prescribed, neither do we know how good the compliance of patients was with the treatment. Thirdly, once the patients are alarmed by an abnormal test, other measures to prevent preterm birth may have been introduced besides taking treatment. Fourthly, the major benefit in prevention was not seen for all prematurely born but only for those in the group of early prematurity (< 32 + 0 weeks, e. g. < 1000 g) and therefore highest perinatal morbidity and mortality. A disadvantage, as discussed by opponents of the method? Rather an unique advantage!

Nevertheless, the broad implication in a whole federal state has led to the positive experience with respect to availability and practicability of a broader approach to prevent preterm birth. Whatever the exact mechanism, the results achieved in the study region Thuringia in 2000 are the best ever seen in any of the German states in the past! Indeed, after discontinuation of the campaign due to financial limitations, the prematurity rates in Thuringia immediately rose again to previous levels remaining at the same level in the subsequent years (Table 2).

Table 2. Distribution of Birthweights (%) State of Thuringia 1999-2005. *p < 0.05, **p < 0.01, ***p < 0.001

Year	1999	I/2000	**II/2000**	2001	2002	2003	2004	2005
N	16233	8162	**8458**	16408	15995	15436	16058	15633
< 1000g	0.54	0.61*	**0.38**	0.46	0.63***	0.62**	0.60**	0.56**
< 1500g	1.22**	1.29*	**0.97**	1.09	1.32**	1.17*	1.15*	1.30**
< 2000g	2.67***	2.67*	**2.03**	2.36**	2.62***	2.74***	2.34**	2.60***
< 2500g	6.76***	6.91**	**5.99**	6.64***	6.72***	6.80***	6.35**	6.88***
<1000g	Perinatal Center Erfurt	1.5	**1.0**	1.5	1.6	1.5	1.4	1.7

Outlook

Prevention of preterm birth by screening, diagnosis and antimicrobial therapy of genital infections should be implicated as a necessary step for optimizing and rationalizing health care systems in general.

A controlled, prospectively randomised study addressing pH self-measurement and diagnosis as well as subsequent and adequate treatment is still required but almost impossible to perform. On the other hand, since less is more, further progress can also be expected by applying the KISS (Keep it simple, stupid) principle: pH-measuring devices have to become cheaper to produce, more comfortable and simpler to use and to be completely biodegradable before they become an ubiquitous and successful application in developed and underdeveloped countries (Fig.2).

In addition, in another prospective and controlled pH-screening trial of four insurance companies in five German states between 2004 and 2006 odds ratios for early prematurity < 32 + 0 weeks of 0.85 (0.72 – 1.02) and birth weight < 1500 g of 0.79 (0.66 – 0.95) were seen on the basis of 149,082 deliveries monitored.[12]

Figure 2. Paper-cotton pH-EcoCare TM Comfort Swab (Merete Medical) for pH Self-measurement and Simultaneous Set-up of Wet Mount Microscopic Slide by the Gynecologist

Furthermore, the concept of pH self-measurement in particular seems to result in an efficient reduction of prematurity.[3,6,8,10] The chance to reduce the extremely costly complications associated with preterm birth with minimal expense comes with the fact that the immeasurable extraordinary strain on all parties involved can be reduced in a beneficial way. Can we as physicians, health care providers and politicians take the liberty to ignore these encouraging prospects?

References

1. ***Hitti J, Watts DH***: *Bacterial sexually transmitted infections in pregnancy; in Holmes KK, et al (eds): Sexually Transmitted Diseases, ed 4. New York, McGraw Hill, 2008, pp 1529-1561.*

2. ***Larsson PG, Platz-Christensen JJ, Thejls H, Forsum U, Pahlson C***: *Incidence of pelvic inflammatory disease after firsttrimester legal abortion in women with bacterial vaginosis after treatment with metronidazole: A double-blind, randomized study. Am J Obstet Gynecol 1992; 166: 100-103.*

3. ***Hoyme UB, Saling E***: *Efficient prematurity prevention is possible by pH-self measurement and immediate therapy of threatening ascending infection. Eur J Obstet Gynecol Reprod Biol 115 (2004) 148-153.*

4. ***Hillier SL, Nugent R, Eschenbach DA, Krohn MA, Gibbs RS, Martin DH, Cotch MF, Edelman R, Pastorek JG, Rao AV, McNellis D, Regan JA, Carey JC, Klebanoff MA***: *Association between bacterial vaginosis and preterm delivery of a low-birth-weight infant. N Engl J Med 1995; 26: 1737-1742.*

5. ***Saling E, Fuhr N, Placht A, Schumacher E***: *Erste Resultate der "Selbstvorsorge-Aktion von Schwangeren" zur Frühgeburtenvermeidung. Arch Gynecol Obstet 1995; 257: 178–185.*

6. ***Donders DD, Calsteren van K, Bellen G, Reybrouck R, Bosch van den T, Riphagen I, Lierde van S***: *Predictive value for preterm birth of abnormal vaginal flora, bacterial vaginsosis and aerobic vaginitis during the first trimester of pregnancy. BJOG 2009; 116: 1315-1324.*

7. ***Mc Gregor JA, French JI, Seo K***: *Adjunctive clindamycin therapy for preterm labor: Results of a double-blind, placebo-controlled trial. Am J Obstet Gynecol 1991; 165: 867– 875.*

8. ***Kiss H, Petricevic L, Husslein P***: *Prospective randomised controlled trial of an infection screening programme to reduce the rate of preterm delivery. BMJ 2004; 329: 371-375.*

9. ***Viehweg B, Junghans U, Stepan H, Voigt T, Faber R***: *Der Nutzen vaginaler pH-Messungen für die Erkennung potentieller Frühgeburten. Zentralbl Gynäkol 1997; 119: 33-37.*

10. ***Dennemark N, Meyer-Wilmes M, Schlüter R***: *Screening and treatment of bacterial vaginosis in the early second trimester of pregnancy: a sufficient measure for prevention of preterm deliveries ? Intern J STD AIDS 1997; 8: 38–40.*

11. ***Hoyme UB, Huebner Jana***: *Prevention of Preterm Birth Is Possible by Vaginal pH Screening, Early Diagnosis of Bacterial Vaginosis or Abnormal Vaginal Flora and Treatment. Gynecol Obstet Invest 2010; 70: 286-290.*

12. ***Bitzer Eva-Maria, Schneider, Andrea, Wenzlaff P, Hoyme UB, Siegmund-Schultze, Elisabeth***: *Vaginale pH-Selbstmessung zur Verhinderung von Frühgeburten. Eine prospektive kontrollierte Studie. Dtsch Aerztebl 2011; 6: 81-86.*

Arm Against Recurrent Cystitis!

«European Guidelines on Urological Infections: Grade B recommendation. Level of scientific evidence 1a»[1].

URO-VAXOM®

***E. coli* lyophilized bacterial lysate**

Prescription medication*

Preventive therapy[2]

1 oral daily for 90 consecutive days (3 months)

Prevention can be initiated at the onset or after the antibiotic treatment for the acute infection.

URO-VAXOM® is registered in more than 55 countries worldwide but not in countries such as Italy, France, Spain, UK and the Netherlands.

1. Grabe M. et al. European Association of Urology Guidelines on Urological Infections 2012. www.uroweb.org. **2.** Summary of Product Characteristics.
* Everywhere except in Serbia (OTC status).

URO-VAXOM®: C:lyophilized bacterial lysate: 6 mg. **I:** Immunotherapy. Prevention of recurrent lower urinary tract infections. Comedication in the treatment of acute urinary tract infections. **D:** treatment of acute episodes: 1 caps./day on an empty stomach for at least 10 days; preventive/consolidation therapy: 1 caps./day on an empty stomach for 3 months. **CI:** hypersensitivity to the constituents of Uro-Vaxom. **Pr:** efficacy and safety not tested in children under 4 years. Pregnancy and breast-feeding: no clinical controlled studies available. **AE:** gastrointestinal disorders (diarrhea, nausea, abdominal pain, gastric discomfort, dyspepsia), skin reactions (allergic reactions, rash, pruritus, exanthema), nervous disorders (headache) and generalized problems (slight fever). Treatment should be stopped in case of skin reactions, oedema or fever (possible allergic reactions). 30 and 90 capsules. **For further information, please contact OM Pharma SA.**

OM PHARMA SA · 22 rue du Bois-du-Lan · P.O. Box 88 · 1217 Meyrin 2 / Geneva · Switzerland
www.viforpharma.com

OM Pharma
OM PHARMA SA, A COMPANY OF THE GALENICA GROUP

WHAT'S NEW

Our 'What's New' section of ***European Medical Journal***, aims to provide readers with the latest discoveries, influences and product launches within the field of Gynecology and Obstetrics.

RCOG STATEMENT ON THE PERTUSSIS VACCINE FOR ALL PREGNANT WOMEN

The Royal College of Obstetricians and Gynecologists (RCOG) welcomes the Department of Health's decision to vaccinate all pregnant women in England against pertussis, commonly known as 'whooping cough'. The health ministries in the devolved nations will have similar arrangements.

This follows a sharp increase in the number of cases, especially in babies, earlier this year. Pertussis is an infectious respiratory disease characterised by intense, heavy coughing. Adults who are infected are treated with antibiotics and advised to stay away from others to prevent contagion.

Because their immune systems are still developing, infants are at greater risk of serious complications such as pneumonia which could lead to death if they get whooping cough. For this reason, babies are routinely immunised from the age of two months.

The Department of Health's reason for immunising all women from the 28th week of pregnancy is to enable better protection for all newborns at birth. All pregnant women will now be offered vaccination by their GPs or midwives. RCOG President Dr Tony Falconer said, "This vaccine will ensure that pregnant women and their babies are protected against whooping cough. We would therefore strongly recommend that all pregnant women accept the vaccine when it is offered to them.

"The vaccine is safe for use during pregnancy and there are no known adverse side-effects. If women have any questions, they should speak to their GP or midwife."

THE SIM (SCHMITZ INTEGRATION MODULE) OFFERS GREATER EFFICIENCY IN THE OPERATING THEATRE

Most surgical procedures involve the use of several different items of medical equipment. This is a considerable challenge for the whole operating theatre team - each manufacturer has its own control concept, which team members must learn until it becomes second nature especially in emergencies. This means that intensive training of personnel is necessary – and costly.

The solution is a central system that couples all the devices together. The different components can easily be controlled with a single operating module.

Schmitz and Söhne (a mid-sized manufacturer of medical equipment) is now offering the Schmitz integration module (SiM). This makes it possible to connect their DIAMOND operating table with the OR1™ NEO integration system for operating theatres, manufactured by the Karl Storz company.

The SiM provides enhanced links between the operating table and the central control. Features such as the wireless Bluetooth connection, smart monitoring of operating table movements, and many other electronic functions can now be fully utilised. The module is an innovative step towards lasting and cost-effective organisation of operating theatre procedures.

LEADING CHICAGO PHYSICIAN JOINS GROUNDBREAKING MEDICAL, RESEARCH AND EDUCATION INSTITUTION IN DOHA, QATAR

The Sidra Medical and Research Center in Qatar is re-imagining healthcare for women and children regionally and globally.

Edward Ogata MD, MBA, has been appointed Chief Medical Officer (CMO) at Sidra Medical and Research Center, a groundbreaking medical, research and education institution that focuses on the health and wellbeing of women and children in Doha, Qatar. This key clinical role commenced on September 15, 2012. As the most senior physician at Sidra, Dr. Ogata will provide leadership to the medical staff and lead Sidra to deliver the highest standard of medical care. He will be responsible for implementing strong clinical governance systems, continual quality improvement and ensuring that the quality, safety, efficacy, and efficiency of the clinical services are delivered to the highest level. Dr. Ogata will also ensure that a strong relationship is maintained between Sidra and its faculty members at Weill Cornell Medical College in Qatar, a branch of the prestigious Ivy League university in New York.

"I am honored to be part of this unique project and act as the Chief Medical Officer at Sidra, which I expect will be hugely challenging," said Dr. Ogata. He continued, "It is an extremely exciting prospect to be part of the launch of what will be a world-class hospital facility, and to work to deliver on the Sidra promise to advance and lead with expert medical care for women and children not only in Qatar, but across the whole region."

Dr. Ogata has moved to Sidra from the Ann and Robert Lurie Children's Hospital of Chicago where he was Chief Medical Officer. Dr. Ogata also holds the position of Associate Dean for Academic Affairs, Crown Family Professor of Pediatrics and Professor of Pediatrics at the Northwestern University Feinberg School of Medicine, Chicago. Dr. Ogata has been practicing medicine for over 30 years, specialises in neonatology and his special interests include neonatal hypoglycemia, infants of diabetic mothers, diabetes mellitus and carbohydrate metabolism.

Sidra Medical and Research Center will set new standards in patient care for women and children in Qatar and offer unique and unprecedented opportunities for world-leading health professionals to be pioneers in the discovery and advancement of patient care. The new facility will be all-digital, incorporating the most advanced information technology applications in all clinical, research and business functions.

"We are delighted to welcome Dr. Edward Ogata onboard as Chief Medical Officer of Sidra," commented Dr. Mohammad Fathy Saoud, Vice Chair of Sidra Board of Governors and Chair of Executive Committee. He added, "Dr. Ogata's experience and expertise in top academic medical centres in the US make him perfectly suited to this critical senior leadership role, ensuring that the highest standards in the care of our patients and the advancement of medical research are at the

core of Sidra's unique model, which integrates quality maternal and child health services with medical education and research."

At present, Sidra is working with its partners to finalise exactly when the Medical and Research Center will be fully operational. Patient and staff safety is the highest priority and a rigorous facility and operational commissioning process will be undertaken to ensure that the Center operates at the highest standards.

Q & A With:

Edward S. Ogata, MD
Chief Medical Officer
Sidra Medical and Research Center

Q: What is Sidra Medical and Research Center?

A: Sidra Medical and Research Center will be an ultra-modern, all-digital academic medical center which is being designed and planned to the highest international standards in sciences. It will offer specialty care for women and children. Sidra is committed to providing people living in Qatar and the Gulf region with medical care that ranks with that found in the best healthcare institutions in the world. Sidra's primary focus will be obstetrics, gynecology and a broad spectrum of pediatric services.

Q: What excites you about your new role at Sidra?

A: I am honored to be part of this unique project and I expect it will be hugely challenging. It is extremely exciting to be part of the planning and launch of a groundbreaking hospital facility that will set new standards in patient care for women and children in the region and beyond. I was especially attracted by the opportunity to develop a world-class team of leading health professionals and provide unique and unprecedented opportunities for them to be pioneers in the discovery and advancement of patient care.

Q: What is it like living in Qatar?

A: The Qatari lifestyle is relaxed and very enjoyable - it feels like a home away from home. Qatar ranks 12th in the Global Peace Index, so there is very low crime and there is a friendly and active expatriate community.

Q: How will Sidra affect healthcare in Qatar and the Gulf region?

A: Sidra will set new standards in patient care, education, and research. The services offered will be transformational for the lives of women and children, two historically disadvantaged groups in terms of regional health care. Sidra is part of a dynamic research and education environment in Qatar that includes Sidra's academic partner Weill Cornell Medical College and other international leaders. Through strong partnerships with leading institutions around the world, Sidra is creating an intellectual ecosystem to help advance health care and scientific discovery, and shape the future of health in the Gulf region.

BAYER JOINS GLOBAL INITIATIVE FOR BETTER ACCESS TO EFFECTIVE CONTRACEPTION SUPPORT OF FAMILY PLANNING PROGRAMMES

Long-acting and reversible implant to become available for millions of women living in low-resource nations

A new initiative announced in September at the United Nations headquarters in New York, by Norwegian Prime Minister Jens Stoltenberg, shall make an effective long-acting and reversible contraceptive method (implant) available to more than 27 million women of the world's poorest nations.

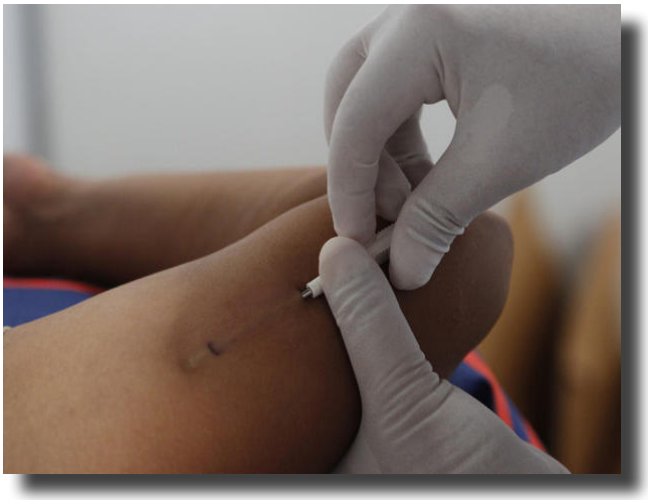
The initiative is a joint effort of the Government of Norway and other partners, including the British and US governments and the Clinton Health Access Initiative, as well as Bayer HealthCare, the manufacturer of the implant.

"Innovation is the key to our commercial success and at the same time the basis of our social commitment," said Dr. Jörg Reinhardt, Chief Executive Officer of Bayer HealthCare AG.

At present, more than 200 million women in developing countries who do not want to get pregnant have no access to modern contraception and family planning services. As a leading company in the field of hormonal contraception, Bayer HealthCare has been working in a network of public and private partners for over 50 years and supports family-planning programs in over 130 countries.

This latest initiative is a further step ahead in this direction. When fully implemented, the new partnership is expected to avert almost 30 million unwanted pregnancies from 2013 to 2019 and will save an estimated 250 million USD in global health costs. It will also help to avert more than 280,000 child and 30,000 maternal deaths.

For Bayer HealthCare, this initiative is part of its "Access to Medicine" strategy, where the company is cooperating with a number of private and state organizations. Through its "Family Planning" and "Neglected Diseases" lighthouse projects, the company is enabling access to health care. The "Family Planning" lighthouse projects also address three of the eight Millennium Development Goals of the United Nations: strengthening equal opportunities, reducing child mortality and improving health care for mothers.



When fully implemented, the new partnership is expected to avert almost 30 million unwanted pregnancies from 2013 to 2019 and will save an estimated 250 million USD in global health costs.

The initiative is targeted at around 42 of the world's poorest countries that have also been targeted by the UN Secretary General's Global Strategy for Women's and Children's Health. These are the countries thought least likely to meet the 2015 Millennium Development Goals set by the UN General Assembly in 1990 to reduce the number of infant and young child deaths by two thirds and to improve maternal health by 2015.

EUROPEAN COMMISSION GIVES GREEN LIGHT TO BAYER HEALTHCARE'S FLEXYESS®

Flexyess is the first combined oral contraceptive with a flexible extended dosing regimen offering women "personal period planning"

Not Intended for U.S and U.K Media

The European Commission has issued its go ahead for the approval of Bayer HealthCare's new low-dose combined oral contraceptive Flexyess. Based on the European Commission's positive decision, the Health Authorities of the EU Member States will grant national approvals in the coming weeks.

Flexyess (3 mg drospirenone/0.02 mg ethinylestradiol) will be the first low-dose combined oral contraceptive approved in the EU member states for a flexible extended regimen, offering women the option of 'personal period planning', meaning they can choose both the number and timing of their periods according to their needs (within the limits permitted by the approved dosing regimen). The new dosing regimen involves a daily intake for a minimum period of 24 days and up to a maximum period of 120 days. During day 25 to 120, women can schedule a 4-day tablet-free interval individually, which triggers the period. This offers the option of flexibly reducing the number of periods to three per year.

"Once Flexyess is launched, women will have the convenience and flexibility to influence the timing of their periods according to their individual needs", said Dr. Flemming Ornskov, Chief Marketing Officer at Bayer HealthCare's Pharmaceuticals division.

Flexyess comes with ClykTM, an innovative digital tablet dispenser that is designed to support women with the new regimen and remind them when to take their pill. The tablet dispenser is expected to improve the adherence to tablet intake because it not only reminds women when to take their pill, but also advises them what to do if they have missed a pill and warns them if additional contraception is needed due to missed pills.

Flexyess provides reliable contraception when taken as directed. It has proven to be effective in preventing pregnancy in clinical studies involving over 2,500 women aged 18-45 years. During the clinical development program, Flexyess was shown to have an overall safety profile that is comparable to the known safety profiles of other oestrogen/progestin containing combined oral contraceptives.

First launches of the product in the EU are expected in the second half of 2013. The name of the combined oral contraceptive can vary from country to country.

NIH RESEARCHERS IDENTIFY NOVEL GENES THAT MAY DRIVE RARE, AGGRESSIVE FORM OF UTERINE CANCER

Serous endometrial tumors account for some of the most difficult to treat cancers of the uterine lining

Researchers have identified several genes that are linked to one of the most lethal forms of uterine cancer, serous endometrial cancer. The researchers describe how three of the genes found in the study are frequently altered in the disease, suggesting that the genes drive the development of tumors. The findings appear in the Oct. 28 2012 advance online issue of Nature Genetics. The team was led by researchers from the National Human Genome Research Institute (NHGRI), part of the National Institutes of Health.

Cancer of the uterine lining, or endometrium, is the most commonly diagnosed gynecological malignancy in the United States. Also called endometrial cancer, it is diagnosed in about 47,000 American women and leads to about 8,000 deaths each year.

Each of its three major subtypes — endometrioid, serous and clear-cell — is caused by a different constellation of genetic alterations and has a different prognosis. Endometrioid tumors make up about 80% of diagnosed tumors. Surgery is often a complete cure for women with the endometrioid subtype, since doctors usually diagnose these cases at an early stage.

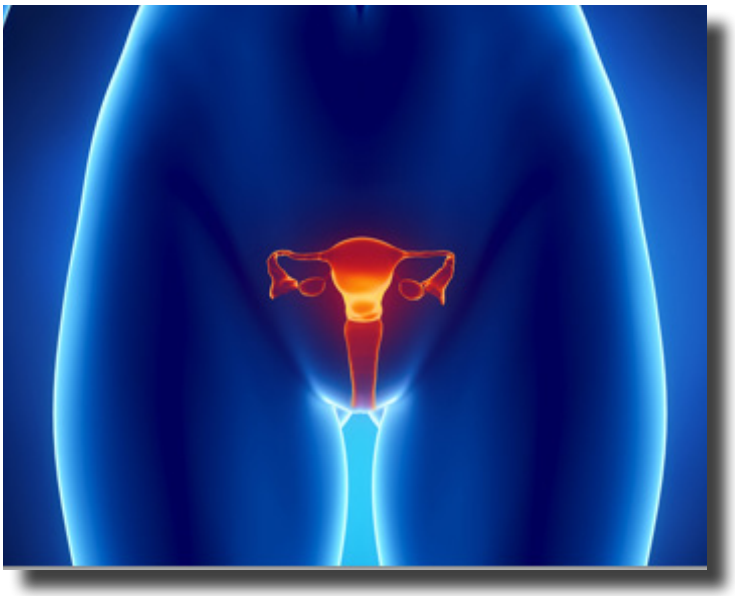
Compared to other subtypes, the 2 to 10% of uterine cancers that comprise the serous subtype do not respond well to therapies. The five-year survival rate for serous endometrial cancer is 45%, compared to 65% for clear-cell and 91% for endometrioid subtypes. Serous and clear-cell endometrial tumor subtypes are clinically aggressive and quickly advance beyond the uterus.

"Serous endometrial tumors can account for as much as 39% of deaths from endometrial cancer," said Daphne W. Bell, Ph.D., an NHGRI investigator and the paper's senior author. Dr. Bell heads the Reproductive Cancer Genetics Section of NHGRI's Cancer Genetics Branch. To determine which genes are altered in serous endometrial cancer, Dr. Bell and her team undertook a comprehensive genomic study of tumors by sequencing their exomes, the critical 1 to 2% of the genome that codes for proteins.

"Exome sequencing is a powerful tool for revealing important insights about this form of cancer that exacts such a high toll for thousands of women," said NHGRI Scientific Director Dan Kastner, M.D., Ph.D. "This study pinpoints genetic alterations that may be essential for onset and progression of uterine cancers and may eventually lead to new therapeutic targets."

Dr. Bell's team focused on the rarer, more aggressive forms of endometrial cancer. They began their study by examining serous tumor tissue and matched normal tissue from 13 patients. National Cancer Institute and Massachusetts General Hospital pathologists processed the 26 tissue samples, which subsequently underwent whole-exome sequencing at the NIH Intramural Sequencing Center.

With the exome data in hand, the researchers filtered through millions of data points to locate alterations, or mutations. They disqualified from the analysis any mutation found in a tumor and its matched healthy tissue, looking expressly for mutations that occurred exclusively in the tumor cells. They also eliminated one of the 13 tumors from analysis because its exome had hundreds more unique mutations than any other tumor.



The researchers detected more than 500 somatic mutations within the remaining 12 tumors. They next looked for genes that were mutated in more than one of the tumors. An alteration that occurs in more than one tumor is more likely to be relevant to the development of the cancer than a unique alteration.

"When you identify a set of mutations, they could either be drivers that have caused the cancer or incidental passengers that are of no consequence; our goal is to identify the drivers," Dr. Bell explained. "One way to do this is to home in on genes that are mutated in more than one tumor, because we know from experience that frequently mutated genes are often driver genes."

The team felt confident that alterations in nine genes could be driver genes in serous endometrial cancer. Three of the nine genes had previously been recognized by researchers in

the cancer genetics field as a cause of serous endometrial cancer. To get a clearer picture of driver gene status among the other six genes, the researchers sequenced each gene in 40 additional serous endometrial tumors. They discovered that three of the six genes — CHD4, FBXW7 and SPOP — are altered at a statistically high frequency in serous endometrial cancer.

The team also found that this set of three genes is mutated in 40% of the serous endometrial cancer tumors and in 15 to 26% of the other endometrial cancer subtypes. Probing still further, the researchers looked for the same genes highlighted by their exome sequencing study within databases that organize genes according to their biological function. They found an enrichment of genes involved in chromatin remodeling, the dynamic process by which the contents of the cell nucleus, including DNA, are packaged and modified. Chromatin remodeling enables tightly packaged DNA to be accessed for the expression of genes. Intriguingly, CHD4 was one of the genes that formed the chromatin-remodeling cluster.

"We sequenced the other genes that make up this cluster and, as a set, these genes are frequently mutated in both serous and clear-cell endometrial tumors," said Dr. Bell. They also noted frequent mutations in genes that regulate a process known as ubiquitin-mediated protein degradation. The process targets unneeded proteins for destruction, and thus prevents them from accumulating within the cell. Left to accumulate, some of the target proteins are known to drive cancer formation. FBXW7 and SPOP are both known to play a role in binding to the unneeded proteins and targeting them for destruction.

Many of the FBXW7 gene mutations that Dr. Bell's team identified are known in other cancers to be driver mutations that prevent the FBXW7 protein from binding to its target protein. Dr. Bell believes that altered SPOP may behave the same way. "All the mutations we found in SPOP are in the region that binds the target proteins" she said. "We suspect the mutations in SPOP might lead to the accumulation of the unneeded proteins within the cell. But that has to be tested."

The current findings build on the team's 2011 study that showed for the first time that alterations in the PIK3R1 gene occur in all subtypes of endometrial cancer and are most frequent in the more common endometrioid subtype.

"This discovery really changes our understanding of some of the genetic alterations that may contribute to this disease," Dr. Bell said, acknowledging that the findings are limited by the small number of tumors subjected to exome sequencing. She noted that it is too early to make a direct connection between their findings and prospects for treatments for this aggressive form of uterine cancer.

Buyer'sGuide

FeaturedSuppliers

Alere International Ltd has diagnostic tests available for pre-eclampsia, preterm labour, PROM, STD screening, bone health, vaginal infections, and pregnancy testing.

Bayer Healthcare Pharmaceuticals is the world leader in the field of female hormonal contraception. In the gynecological therapy segment, the company is working to develop new therapeutic options for conditions with a high level of unmet medical need such as uterine fibroids (myomas) and endometriosis.

Biolitic® introduces a revolutionary laser system that together with dedicated fibers optics and accessories allows you to expand your practice in different areas of gynecology.

Gedeon Richter Plc. is an innovation-driven specialty pharmaceutical multinational whose activities include pharmaceutical manufacturing, research and development, sales and marketing. Original research activity focuses on CNS disorders, mainly schizophrenia, chronic pain and depression, and gynecology.

GlaxoSmithKline Vaccines is one of the world's leading vaccine companies and a leader in innovation. The company is active in vaccine research, development and production with over 30 vaccines approved and 20 more in development.

Sanofi Pasteur MSD is dedicated exclusively to vaccines in the belief that prevention is better than cure and immunisation is the best prevention. Their vaccines help protect people from 20 infectious diseases including cervical cancer, liver cancer, tuberculosis, measles, yellow fever, shingles and influenza.

Vifor Pharma and OM Pharma (Switzerland) are amongst the world leaders in iron preparations for iron deficiency and immunoactive therapies such as recurrent cystitis prevention.

Associations

Associazione Italiana Cistite Interstiziale – ONLUS	www.aicionlus.org
International Society of Gynecological Endocrinology	www.gynecologicalendocrinology.org
European Board and College of Obstetrics and Gynaecology (EBCOG)	www.ebcog.eu
Exelgyn SAS	www.exelgyn.com
Flight For Every Mother	www.flightforeverymother.com
PRONTO International	www.prontointernational.org
Ipas	www.ipas.org
International Urogynecological Association	www.iuga.org
Japan Society of Obstetrics and Gynecology	www.jsog.or.jp
Jhpiego – an affiliate of Johns Hopkins University	www.jhpiego.org
Laerdal Global Health AS	www.laerdalglobalhealth.com
Liverpool School of Tropical Medicine Maternal and Newborn Health Unit	www.mnhu.org
Medecins Sans Frontieres (MSF)	www.msf.org
Partnership for Maternal, Newborn and Child Birth	www.who.int
Save The Children	www.savethechildren.org
The Global Library of Women's Medicine	www.glowm.com
The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)	www.ranzcog.edu.au

Buyer'sGuide

3B Scientific GmbH	www.3bscientific.com
AB Medica Spa	www.abmedica.it
ACRAF S.p.A	www.angelini.it
AgPharma srl	www.agpharma.com
AmniSure	www.amnisure.com
ATMOS MedizinTechnik	www.atmosmed.de
Avantgarde S.p.A	www.avantgardepharma.com
Besins Healthcare	www.besins-healthcare.com
Biolive SRL	www.alpinionitalia.it
Boehringer Ingelheim Pharma GmbH & Co.	www.boehringer-ingelheim.com
BOWA-electronic	www.bowa.de
Cepheid	www.cepheidinternational.com
Clinical Innovations	www.clinicalinnovations.com
Dale Medical Products	www.dalemed.com
DEKA	www.dekalaser.com
Dermasilk - Alpretec	www.dermasilkintimo.com
Doctor Shop Srl	www.doctorshop.it
EchoHeart, Inc.	www.echoheart.com
ECM	www.agroscan.com
EMED SP	www.emed.pl
ERBE Elektromedizin GmbH	www.erbe-med.com
Euroclinic S.p.A	www.euroclinic.it
Femcare-Nikomed Ltd	www.femcare-nikomed.co.uk
Fotona	www.fotona.com
Fujirebio Diagnostics AB	ww.fdab.com
Gaumard Scientific Co. Inc	www.gaumard.com
GE Healthcare	www.gehealthcare.com
Group B Strep International	www.groupbstrepinternational.org
Guided Therapeutics	www.guidedinc.com
Gynius AB	www.gynocular.com
Hologic Inc.	www.hologic.com

GYNECOLOGY & OBSTETRICS

Huntleigh Healthcare Ltd	www.huntleigh-diagnostics.com
IBSA Institut Biochimique SA	www.ibsa-international.com
Idipharma	www.idipharma.com
Johnson & Johnson Medical SpA	www.jnj.com
Karl Storz GmbH & Co.HG	www.karlstorz.de
Laborest Italia SpA	www.laborest.com
MedGyn Products, Inc	www.medgyn.com
Medicem	www.medicem.com
Medix Biochemica	www.medixbiochemica.com
Medica S.p.A	www.medica.it
Nycomed: a Takeda Company	www.nycomed.com
Olympus Europa Holding GmbH	www.olympus-europa.com
Omega Pharma Italia	www.chefaro.it
Pelican Feminine Healthcare Ltd	www.pelicanfh.co.uk
Pfizer, Inc.	www.pfizer.com
Philips Healthcare	www.philips.com/motherandchild
Pierre Fabre	www.pierre-fabre.com
Prothia	www.prothia.fr
Richard Wolf GmbH	www.richard-wolf.com
RI.MOS. Srl	www.rimos.com
Schmitz Italia s.r.l	www.schmitz-italia.it
SIUI	www.siui.com
Sidra Medical and Research Center	www.sidra.org
Siemens AG Healthcare Sector	www.siemens.com/ultrasound
Sofar S.p.A	www.sofarfarm.it
SPD Swiss Precision Diagnostics GmbH	www.clearblue.com
Surgical Science AB	www.surgical-science.com
Theramex/Teva	www.theramex.mc
Toshiba Medical Systems	www.toshiba-medical.eu
Uniderm Farmaceutici Srl	www.uniderm.it
Wallach Surgical Devices	www.wallachsurgical.com
Zenex Medtech	www.dundex.com

www.emjreviews.com

Please click **here** to subscribe and receive the latest updates and publications from EMJ

From a host of fourteen therapeutical areas, *European Medical Journal* provides **influential articles**, presentations of **up-to-date scientific research** and clinical practice and **in-depth reviews** of international medical congresses.

Click **here** to view each edition in convenient eBook format.

If you are interested in submitting a paper to EMJ please contact **editor@congressreviews.com**

You can also find us on **Facebook**, **LinkedIn** and **Twitter**

Irritation, itching, pain and burning in the genital area? Today, research has produced a new weapon for fighting these troublesome symptoms. It isn't a medicine or even a cream, but a pair of briefs: **DermaSilk® INTIMO.**

It seems incredible but it isn't, if two scientific journals of the calibre of Mycoses and the Journal of Lower Genital Tract Disease have published two clinical studies demonstrating the usefulness of these special garments in reducing these symptoms even in notoriously "tricky" pathologies such as Recurrent Vulvovaginal Thrush and Vulvar Lichen Sclerosus.

But what is the secret of these briefs?
The secret lies in an original combination of Nature and High Technology. DermaSilk briefs are made of silk fibroin, the noblest and purest part of this precious natural fibre, and they are protected by a permanent non-migrating antimicrobial agent which inhibits the growth of pathogenic microorganisms on the fabric and controls unpleasant smells, without altering the resident flora. The result is an extraordinarily pure and microbiologically protected natural fabric. But that's not all: this fabric is incredibly similar to our own skin, able to protect it and to favour its equilibrium and functions, even when they are compromised. Silk fibroin has a chemical protein structure very similar to the stratum corneum (the outermost layer of the skin and mucosa), recognised as one of the major skin growth factors.

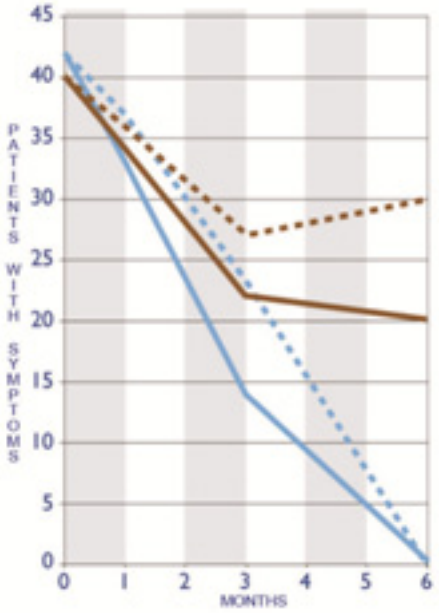
DermaSilk briefs favour the equilibrium of the skin and mucosa and respect the vulvovaginal ecosystem thanks to a number of important characteristics, such as high breathability guaranteed by the special knitting process, heat regulation which maintains the correct body temperature and a high hygroscopic capacity, thanks to which the fabric is able to retain up to 30% of its own weight in humidity, remaining dry and rapidly eliminating the excess humidity.

These characteristics are fundamental for the good health of the genital area, which more than others requires good ventilation and fears increased temperature and humidity, factors which favour the growth of pathogenic microorganisms and the onset of infections such as Candida (the negative action of panty liners, non-breathing underwear, polyamide briefs, tight pantyhose and trousers is well known).

Available in various models to satisfy the personal taste of every woman, DermaSilk briefs can be a useful additional tool in the prevention and treatment of vulvitis but also a valid aid in the case of disturbances such as itching, irritation or dryness, which are not necessarily linked to a pathology but may arise from imbalances of a hormonal nature (e.g. menopause, pregnancy) or an immune nature, or even from stress and incorrect habits (aggressive detergents, non-breathing garments, etc.).

"The evidence put together in the multimodal therapy of atopic dermatitis and the evidence emerging in the field of vulvar dermatology suggests that knitted fabric of medicated natural silk, consisting of 100% fibroin without sericin and ennobled with a permanent non-migrating antimicrobial agent with a base of quaternary ammonium, may be a valid tool for the prevention and therapy of mycotic and bacterial vulvitis and of Lichen Sclerosus, to be included among the multimodal treatment strategies appropriate for these pathologies"*(1).

A study published on the scientific journal ***Mycoses*** "**Use of DermaSilk briefs in recurrent vaginal thrush: safety and efficiency**" *(2), carried out on 96 women, has shown that the use of DermaSilk INTIMO briefs, in comparison with pure cotton underwear (with the same standard therapy), not only helps to reduce the symptoms of itching, burning and pain in a short time, but also decreases the number of relapses. This is very important, considering that 75% of women have at least one episode of vaginal thrush in their lifetime and up to 50% of these report recurring episodes.



Excellent results have also be obtained in the paediatric field.

In a study published in the ***Giornale Italiano di Dermatologia e Venereologia*** carried out on a group of pre-pubertal girls with recurrent inflammatory vulvitis (at least 3 episodes in the 3 months prior to the start of the study, DermaSilk underwear proved useful both in cases of infective vulvitis (1/3) – combined with the standard treatment – and in cases of non-specific irritative vulvitis (2/3), where it was not associated with any pharmacological therapy "(…) DermaSilk® briefs proved to play an important role in the management of flares (…), as shown by an earlier resolution of symptoms, as well as in the maintenance of remission and in the prevention of superinfections (…)"* (3). In fact, none of the girls had any relapses after starting to use DermaSilk INTIMO briefs.

DermaSilk INTIMO has also proved to be an important additional tool in the treatment of **Vulvar Lichen Sclerosus**, a pathology recognised among rare diseases that are unfortunately becoming more and more widespread, in both the female and the male population.

The study published in the ***Journal of Lower Genital Tract Disease*** compared DermaSilk INTIMO briefs with pure cotton briefs (with the same standard therapy). The results shows that "(…) the patients in the DermaSilk group, in comparison with those in the Cotton group, reported a more rapid response to treatment with a lower severity score for itching and burning after one month of treatment (...)"* (4). As may be seen from the table, at the end of the study none of the women who had used DermaSilk had any more itching or pain. More than half had also overcome burning, dyspareunia (pain during intercourse) and erythema, resulting in a considerable

	DERMASILK GROUP		COTTON	
	Number of patients at the beginning of study (baseline)	Number of Patients after 6 months	Number of patients at the beginning of study (baseline)	Number of Patients after 6 months
ITCH	13	0	14	4
PAIN	20	0	19	16
BURNING	21	9	21	21
DYSPAREUNIA	20	9	16	16
ERYTHEMA	21	9	21	19

DermaSilk® INTIMO

The DermaSilk® INTIMO line comprises more than 30 variants in size and style: various models of Briefs and Bra for Women, Boxer shorts and Briefs for Men, and Briefs for Girls and Boys.

DermaSilk INTIMO is PATENTED and MANUFACTURED by ALPRETEC Srl, an Italian company certified according to ISO 9001:2008 and specialised in high-tech fabrics for health.
DermaSilk INTIMO is a Class 1 Medical Device.

The **DermaSilk INTIMO** line was presented for the first time in November 2010 at the SIGO-AOGOI National Congress (Italian Society of Gynaecology and Obstetrics – Association of Italian Hospital Obstetricians and Gynaecologists) Milan, Italy, but it **springs from the already known and acknowledged DermaSilk line of therapeutic clothing (Class 1 Medical Device), included in the European Guidelines for the treatment of Atopic Dermatitis and refunded by the National Health Service and by Private Insurance Schemes in many European countries** (e.g. United Kingdom, Netherlands, Switzerland, Sweden and Austria).

DermaSilk INTIMO has official distributors in Australia/New Zealand, Austria, Belgium/Luxembourg, Canada, Denmark, Greece, The Netherlands, Poland, Romania, Sweden/Norway/Finland, Switzerland, and United Kingdom/Ireland. In Italy DermaSilk INTIMO briefs are distributed directly by the manufacturer as in Countries not covered by an official distributor.

All information on **www.dermasilkintimo.com**

Bibliography

*(1) Graziottin A., Murina F., " Vulvodinia. Strategie di Diagnosi e Cura" da Appendice: "Il tessuto che cura". Book published by Springer-Verlag Italy 2011.

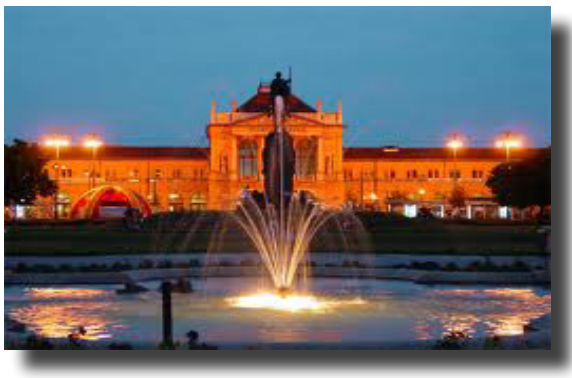
*(2) D'Antuono A. et al., - Clinica Dermatologica Università di Bologna -, "Use of DermaSilk briefs in recurrent vulvovaginal candidosis: safety and effectiveness" – published on Mycoses, 2011; Volume 55; Issue 3:e85-e89. Six-month study carried out on 96 women undergoing standard treatment and divided into two groups (DermaSilk Group and comparison with Cotton Group).

*(3) Patrizi A. et al., - Clinica Dermatologica Università di Bologna -, "Clinical effectiveness of a special silk textile in the treatment of recurrent pediatric inflammatory vulvitis: an open label pilot study" - published on Giornale Italiano di Dermatologia e Venereologia, 2011; Volume 146; No.5: 317-320. Study carried out on 12 pre-pubertal girls undergoing standard treatment and using DermaSilk briefs.

*(4) D'Antuono A. et al., - Clinica Dermatologica Università di Bologna - "DermaSilk Briefs in Vulvar Lichen Sclerosus: An Adjuvant Tool" - published in Journal of Lower Genital Tract Disease, 2011 (American Society for Colposcopy and Cervical Pathology); Volume 15, Number 4: 287-291. Six-month study carried out on 42 women undergoing standard therapy and divided into two groups (DermaSilk Group and comparison with Cotton Group).

1st International Congress and 2nd Croatian Symposium on the Prevention and Treatment of Early Cervical Cancer

January 24-26, 2013
Zagreb, Croatia



The congress will discuss contemporary views on prevention of HPV, responsible sexual behaviour, educating youth and the need to introduce systematic health education in schools, vaccination against HPV, the initial diagnosis and treatment of cervical cancer and the necessity of going for regular pelvic exams with PAP assay.

9th International Symposium on Advanced Ovarian Cancer: Optimal Therapy Update

March 01, 2013
Valencia, Spain

The International Congress on Oncological Perspectives of Fertility Preservation: Gynecological & Breast Cancer (OP/FP)

March 21-23, 2013
Berlin, Germany

In this congress, new technologies in cryopreservation, chemotherapy, radiation and surgical procedures will be discussed in order to provide clear insights into possible treatments for this specific patient group—people who want to maintain normal lives despite battling with the aftermath of cancer. This educational congress benefits not only oncologists, but also general gynecological practitioners wishing to gain knowledge in exciting fertility preservation advancements.

First Global Conference on Contraception, Reproductive and Sexual Health

May 22-25, 2013
Copenhagen, Denmark

Our aim through this congress is to open up new and global avenues of research and enquiry to promote sexual health care with focus also on regional differences, cultural and political diversities as well as new technologies. The Congress will consist of informative sessions, interactive discussions and symposia that will be conducted by opinion leaders sharing the latest discoveries in all aspects of the field according to the ESC tradition.

UPCOMING EVENTS &CONGRESSES

The World Congress on Building Consensus out of Controversies in Gynecology, Infertility and Perinatology (BCGIP-cogi)

May 30-June 2, 2013
Istanbul, Turkey

The Congress will promote excellence in the fields of Gynecology, Obstetrics, Infertility and Perinatology and aim to bridge gaps between the expansion of information and its implementation in clinical practice. International and local experts will share and compare experiences in stimulating and interactive debates. Allowing ample time for speaker-audience discussion, the Congress aims at reaching up-to-date and agreed-upon answers to ongoing debates even when proof is lacking, through evidence-based medicine and expert opinion.

Royal College of Obstetricians and Gynecologists World Congress 2013

24-26 June 2013
Liverpool, England

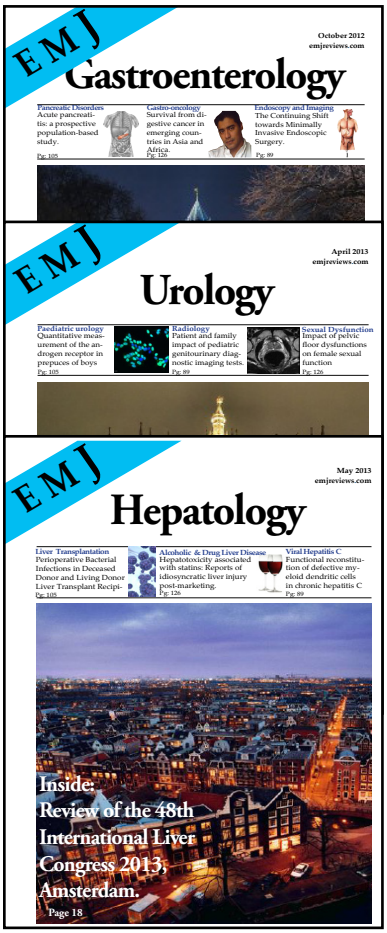
10th Congress of the European Society of Gynecology

18-21 September 2013
Brussels, Belgium

This Congress will be a platform for extensive exchanges about many aspects of women's health, reproductive medicine and obstetrical complications. Plenary presentations and keynote lectures will provide integrated and up to date comprehensive information about the recent therapeutic achievements and present knowledge in Gynecology and European medical Consensus.

www.emjreviews.com

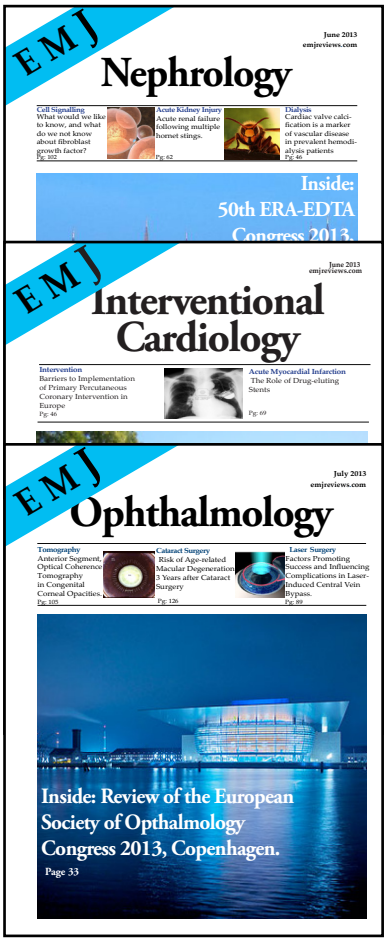
"providing professionals with the most salient and up-to-the-minute developments"



Visit our website to view all of our titles in convenient eBook format.

"A lively mix of review articles, case reports, practice guides, theoretical discussions and original research will ensure that readers are kept informed, and will also stimulate healthy discussion between specialties - the mark of a quality publication"

Professor Hamid Rushwan, FIGO Chief Executive.



To subscribe and receive the latest updates and publications from EMJ go to:

www.emjreviews.com

If you are interested in submitting a paper to EMJ please contact:

editor@congressreviews.com

You can also find us on:

Facebook, **LinkedIn** and **Twitter**