TREATMENT STRATEGIES

Obstetrics and Gynaecology

Volume 1 Issue 1

- Cervical Cancer
- Endometrial Cancer
- Female Sexual Dysfunction
- Gynaecologic Endocrinology
- Ovarian Cancer
- Pregnancy

Articles include:

Image Guided Adaptive Brachytherapy in Locally Advanced Cervical Cancers: Preliminary Results and Perspectives

Targeting Elements of the Epithelial Growth Factor Receptor Pathway in Persistent and Recurrent Cancers of the Uterine Cervix

Sexual Dysfuction in Women with Diabetes

Adjuvant Treatment Paradigms in Endometrial Adenocarcinoma

Cancer During Pregnancy: Interim Data From a Preclinical and Clinical Study

Angiogenesis: A Target for the Treatment of Ovarian Cancer

FIGO ROME 2012

Includes a review of the FIGO 2012 World Congress

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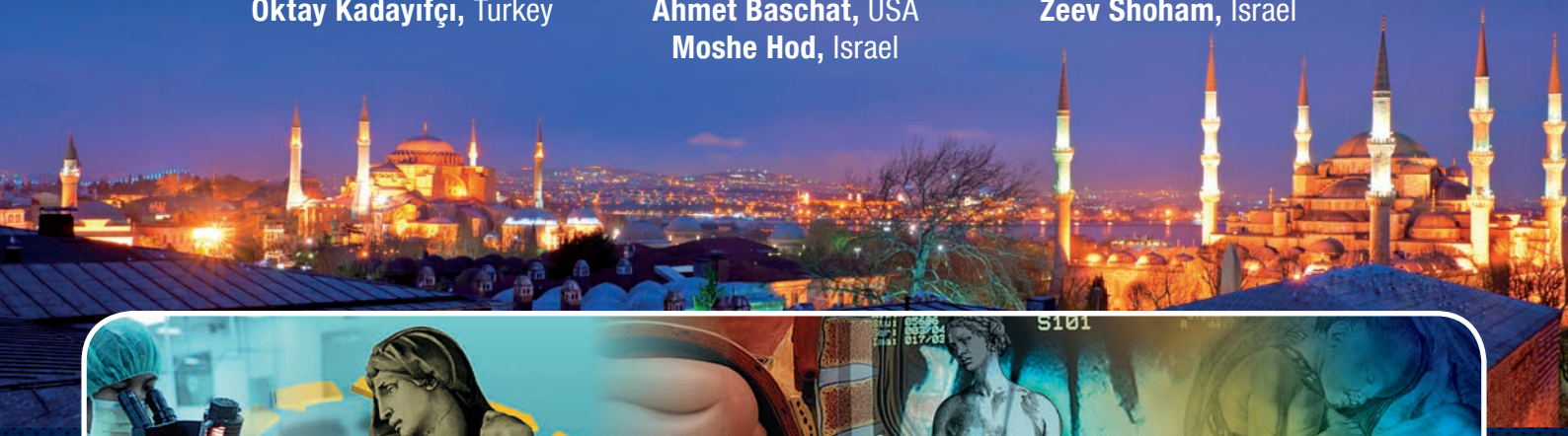

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TREATMENT STRATEGIES
Obstetrics and Gynaecology

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Welcome...

A very warm welcome to the inaugural edition of *Treatment Strategies - Obstetrics and Gynaecology*. This edition will address the key topical areas in the obstetrics and gynaecological field and feature an exciting collection of papers from esteemed specialists.

Treatment Strategies - Obstetrics and Gynaecology will include papers on topics such as pregnancy, female sexual dysfunction, gynaecologic endocrinology and cervical cancer, amongst others. We hope that this publication will provide you with a comprehensive review of the latest updates and advances in obstetric and gynaecological medicine.

Following on from a successful visit to Rome, we have also included a review of the latest developments from last year's World Congress of The International Federation of Gynecology and Obstetrics (FIGO). FIGO is the only worldwide organisation that groups obstetricians and gynaecologists. It has member associations in 125 countries.

FIGO's mission is to promote the wellbeing of women and to raise the standards of practice in obstetrics and gynaecology. Through the work of dedicated Committees and Working Groups, FIGO's work embraces many aspects of obstetrics and gynaecology such as oncology, STDs/AIDS, perinatal health, education, safe motherhood, medical terminology, women physicians in the specialty, social activities on women's health, new technology, the pathology of the breast and ethics.

We hope that this information will be informative for the readers and will serve as a forum in which to present the constantly evolving and developing findings from the obstetrics and gynaecology field. We do hope that you will find the publication interesting and we look forward to hearing your feedback to help maintain the high standards of the series. With your contribution we will ensure that the *Treatment Strategies* series becomes one of the most useful publications in healthcare.

We look forward to meeting you at the next FIGO World Congress in Vancouver in 2015.

Nigel Lloyd, Managing Director

The Cambridge Research Centre wishes to thank the following societies for their assistance and involvement in this publication.

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Foreword

Luis Cabero Roura
Chair of the Education and Training and Capacity Building Committee, International Federation of Gynecology and Obstetrics (FIGO)

I would like to wish you a very warm welcome to the inaugural edition of *Treatment Strategies - Obstetrics and Gynaecology*. Within this publication we hope to bring to you the very best articles relating to all manner of women's health issues, as well as an in-depth review of the International Federation of Gynecology and Obstetrics (FIGO) 2012.

The education, preparation and training of professionals are fundamental to the improvement of women's sexual and reproductive health indicators. Preparation guides the individual to the acquisition of knowledge for a specific task, training guides the development of specific skills and abilities to carry out tasks and education is the acquisition of knowledge in preparation for further learning.

Capacity building is a conceptual approach to development that focuses on understanding the obstacles that inhibit people, governments, international organisations and non-governmental organisations from realising their developmental goals while enhancing the abilities that will allow them to achieve measurable and sustainable results. The term capacity building emerged in the lexicon of international development during the 1990s and often refers to strengthening the skills, instincts, competencies and abilities of people and communities in developing societies so they can overcome the causes of their exclusion and suffering. Capacity building is much more than training.

FIGO is dedicated to the improvement of women's health and rights and to the reduction of disparities in health care available to women and newborns as well as to advancing the science and practice of obstetrics and gynaecology. The organisation pursues its mission through advocacy, programmatic activities, capacity strengthening of member associations and education and training. For that reason FIGO is committed to:

- Continually upgrading the practice of gynaecology and obstetrics and maintaining the highest levels of professionalism and ethical standards through education and training.
- Encouraging all efforts to raise the status of women and advancing their role in all issues related to women's health.
- Promoting sexual and reproductive health rights and services through education, research and advocacy as well as through the provision of accessible, efficient, affordable, comprehensive reproductive health services.

Strengthening communication with and between member associations and building the capabilities and capacity of those from low-resource countries through strengthening leadership, management, good practice and the promotion of policy dialogues to enable societies to play a pivotal role in the development and implementation of projects and policies aimed at the improvement of care available to women and newborns.

The FIGO Committee Capacity Building in Education and Training (CBETC) is the responsible for all these educational and training activities. The vision of the CBETC is that all countries of the world will have effective educational and training programs that increase the professional capabilities of women's healthcare professionals and enable them to continue to increase their own professional.

The CBETC is based on the structure of FIGO itself and shares its values. The values of the organisation being those of innovative leadership, integrity, transparency, professionalism, respect for cultural diversity and high scientific and ethical standards. The Committee's activities, according to its Terms of Reference, are carried out in collaboration with National Societies. All involved have recognised that the education, preparation and training of professionals are essential to the improvement of women's sexual and reproductive health indicators.

Luis Cabero Roura graduated from medical school specialising in Obstetrics and Gynaecology. He completed his PhD degree in Medicine and Surgeons and a second PhD degree in Biological Sciences. He is currently Head of the Department of Obstetrics and Gynaecology at Hospital Materno-infantil Valle Hebron and Chairman of the Department of Obstetrics and Gynaecology at University Autonomous in Barcelona.

Prof Cabero has served as the President of the Spanish Society of Gynaecology and Obstetricians (SEGO), President of the Federation of Associations Scientific-Medical España (FACME) and President of the Comisión Nacional de la Especialidad (Board of the Specialty in Obstetrics and Gynaecology) of Gynaecology and Obstetrics at the Ministry of Health. He also served as President of the Baby Friend Hospitals of UNICEF-Spain and Vice-President of the Fundación Esclerosis Múltiple. Prof Cabero is also Chairman of the Educational Group of the European Association of Perinatal Medicine and a member of the Executive Committee of European Board and College of Obstetrics and Gynecology. He was President of FIGO Scientific Comité Chile and is a member of the Board of the Federation International of Gynecologists and Obstetrics (FIGO). He also served as Vice-President of FIGO from 2003 to 2006.

FIGO 2012 World Congress Review

07 - 12 October 2012 - Rome

The World Congress of The International Federation of Gynecology and Obstetrics (FIGO) — Review

INSIDE...

The Meeting

The Exhibition

Lauran Elsden, Editorial Assistant, *Treatment Strategies*, takes a look over a number of key sessions, as well as spotlighting several stands and products being demonstrated at the exhibition. We then follow with papers and reviews which give a brief insight from a number of sessions highlighting findings that will have direct repercussions on clinical practise that are still very much being discussed.

The International Federation of Gynecology and Obstetrics (FIGO) is the only worldwide organisation that groups obstetricians and gynecologists. It has member associations in 125 countries/territories. Its Secretariat is based in London, in the UK.

FIGO's mission is to promote the wellbeing of women and to raise the standards of practice in obstetrics and gynecology. Through the work of dedicated Committees and Working Groups, FIGO's work embraces many aspects of obstetrics and gynecology such as oncology, STDs/AIDS, perinatal health, education, safe motherhood, medical terminology, women physicians in the specialty, social activities on women's health, new technology, the pathology of the breast and ethics.

It has grown from an organisation representing 42 national societies - who attended the founding meeting on 26 July 1954 in Geneva, Switzerland - into a truly global organisation. It is a benevolent, non-profit organisation funded through subscriptions received from member societies, grants and the proceeds of its triennial World Congress.

Every three years since FIGO's founding in 1954, thousands of gynecologists and obstetricians gather in one city to spend a week analysing and discussing new medical discoveries and looking at problems and issues that can be addressed by the application of low-cost techniques. The site for the World Congress rotates between the Africa-Eastern Mediterranean, Asia-Oceania, Europe, Latin America and North America regions of FIGO.

The beautifil Roman Forum.

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The site is selected six years in advance by a majority vote at the General Assembly.

The 2012 FIGO World Congress took place in Rome, Italy, at the Fiera di Roma, from 7-12 October 2012. Rome was selected from a shortlist of seven European cities by the FIGO General Assembly on 9 November 2006.

Considered by many to be the birthplace of Western civilisation, Italy's capital city Rome brings together culture, beauty and history that dates back over two and a half thousand years. When visiting Rome it is difficult to decide what to see or do first. The Colosseum, Trevi Fountain, Pantheon and the Arch of Constantine constitute only a handful of the many examples of breathtaking classical architecture Rome has to offer. As a predominantly Roman Catholic city, Rome is also home to a host of remarkable and unmissable religious buildings including the city's cathedral Basilica of St. John Lateran, the Church of the Gesù and the Catacombs of Rome.

Architecture aside, Rome also contains a vast and impressive collection of art, sculpture, fountains, mosaics, frescos, and paintings, from many different periods. And if you're partial to sampling different cuisines Rome offers possibilities for every pocket and every mood. There are hip spots that attract fashionable crowds, haute cuisine restaurants, countless pizzerias, and popular eateries called "trattorie". Of course there is ample opportunity for a nice glass of wine too!

Rome is a noisy, chaotic, bustling city but offers an experience no other place can offer. The only difficultly in visiting is how to fit everything in!

This year's FIGO Meeting was located in Fiera di Roma. Inaugurated in April 2006, and representing one of the largest and most prestigious exhibition destinations in Europe, Fiera Roma proved to be an excellent host to the FIGO 2012 Meeting.

"FIGO, the International Federation of Gynecology and Obstetrics, has a vision that women of the world achieve the highest possible standard of physical, mental, reproductive and sexual health and wellbeing throughout their lives. Our mission is dedicated to the improvement of women's health and rights and to the reduction of disparities in health care available to women and newborns, as well as to advancing the science and practice of obstetrics and gynecology."

Professor Gamal Serour, President of FIGO, inaugurated the opening press conference of the FIGO 2012 World Congress of Gynecology and Obstetrics in Rome, Italy

The FIGO LOGIC Initiative: Working Towards Better Maternal and Newborn Health

"Despite combined efforts and recent progress, the targets set by the United Nations to reduce by two-thirds, between 1990 and 2015, the under-five mortality rate and by three-quarters the maternal mortality ratio - known as Millennium Development Goals 4 and 5 - are far from being achieved," said Professor Hamid Rushwan, Chief Executive of the International Federation of Gynecology and Obstetrics (FIGO), presenting the FIGO LOGIC (Leadership in Obstetrics and Gynecology for Impact and Change) Initiative in maternal and newborn health at the XX FIGO World Congress in Rome, Italy.

The LOGIC 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.

In 2009 the FIGO LOGIC Initiative was launched 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.

> **"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."**
>
> **Professor David Taylor, LOGIC Project Director**

"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," he added.

"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%.

FIGO Joining Forces to Achieve the Health-related Millennium Development Goals

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

The FIGO 2012 Congress - held in Europe only once every 15 years, and a first for Italy – gathers over 8,000 participants from across the world: healthcare professionals, leaders from partnership and UN organisations, policy and decision makers, patient groups, and representatives of international media.

"We expect the congress to be a rewarding scientific exchange in many aspects of women's health, from basic to cutting-edge science. We are sure it will also be an occasion 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 Millennium Development Goals," Prof Serour said.

In fact, the vision and mission of FIGO reflect 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 Millennium Development Goals (MDGs) have an impact on women's health - MDG-4 "Reduce child mortality" and MDG-5 "Improve maternal health".

"Professional organisations can do a tremendous amount in this respect, from influencing policy decision-making to raising awareness of issues and their solutions, to setting standards, to educating and training healthcare professionals and providers," he 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 children of every 1,000 dying to 31 of every 1,000.

Since 1990, in the developing regions, the mortality rate of under five years old has declined by 35 percent, from 97 deaths per 1,000 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 20 percent of households.

Maternal mortality has nearly halved since 1990: an estimated 287,000 maternal deaths occurred in 2010 worldwide, a decline of 47 percent 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 percent in 1990 to 71 percent in 2000, and then to 80 percent 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.

"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 health care," Prof Serour concluded.

"FIGO is our natural partner for sexual and reproductive health and reproductive rights. We are together pushing hard to achieve the Millennium Development Goal 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.

"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 the Millennium Development Goals 4 and 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 Organization.

UNAIDS, the Joint United Nations Programme on HIV/AIDS, an innovative partnership that leads and inspires the world in achieving universal access to HIV prevention, treatment, care and support, is a long-term partner of FIGO. "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.

"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."

Frances Day-Stirk,
President of the International Confederation of Midwives

FIGO 2012 Discusses Role of Professional Organisations in Upholding Patients' Rights

Speaking at a session on 8 October titled "The Role of Professional Organisations in Accelerating Progress on Health-Related Millennium Development Goals", UNAIDS Deputy Executive Director, Programme, Dr Paul De Lay highlighted that professional organisations such as FIGO are uniquely placed to take the lead against the mistreatment of patients, especially marginalised women and women living with HIV.

Panellists participating in the FIGO session "The Role of Professional Organisations in Accelerating Progress on Health-Related Millennium Development Goals"

"Professional health organisations have enormous political power, especially where it matters, at the community level," said Dr De Lay. "What the healthcare worker says is accepted and trusted by communities, and professional organisations are uniquely placed to harness that power," he added.

According to participants at the session, patient rights and, particularly in the case of MDG6, the rights of women living with HIV are often ignored. Women living with HIV face enormous challenges in accessing health services. The example of forced sterilisations was mentioned as perhaps the most serious breach of fundamental human rights of women and a cause of major concern among all panellists. Since 2008, cases of forced sterilisation of women living with HIV have been reported, in Chile, the Dominican Republic, Kenya, Mexico, South Africa, Venezuela and Zambia, amongst others. Participants agreed that, failure to address these challenges will result in less women coming forward to access HIV services, less women staying within services and retained on antiretroviral therapy and less women accessing services to prevent HIV transmission to their children.

Professional organisations can take the lead in disseminating up-to-

date information to their members on sexual and reproductive health and rights of women living with HIV, according to the panel. They need to implement strong standards of ethics and conduct for their members. Organisations must ensure that health workers receive training on non-discrimination, informed consent, confidentiality and universal precautions. These organisations also need to ensure that healthcare workers living with HIV are not discriminated against and that they benefit from workplace and treatment programmes.

Professional organisations can serve as a collective workforce towards achieving the health MDGs and also provide a forum to expand knowledge, exchange information and legitimise and amplify the contribution of the members. "Because of their integrity and power, professional associations can be a voice for the voiceless against injustices," concluded Dr De Lay.

UNAIDS Deputy Executive Director, Programme, Dr. Paul De Lay.

"What the healthcare worker says is accepted and trusted by communities, and professional organisations are uniquely placed to harness that power."

UNAIDS Deputy Executive Director, Programme, Dr Paul De Lay

Preliminary Results of the Odon Device Study Presented at FIGO

The preliminary results of the Odon Device study were presented at the 2012 Congress of the International Federation of Obstetrics and Gynecology (FIGO). The Odon device is a new low cost instrument to deliver the foetus when complications occur during the second stage of labour. This device is made of film-like polyethylene material and may be potentially safer and easier to apply than forceps and vacuum extractor (contraindicated in cases of HIV infection) for assisted deliveries, and a safe alternative to some Caesarean sections in settings with limited surgical capacity and human resource constraints.

The Odon Device is being tested in a two-phased study in health care facilities in Argentina and rural South Africa. During phase 1, the device will be tested for safety and feasibility under normal delivery conditions. Testing has already started at a tertiary care centre in Argentina in the context of a WHO approved study. Study results will inform future research to assess effectiveness of the Odon device in reducing negative obstetrical outcomes including newborn infections acquired intrapartum.

Congress participants were also invited to meet Mr. Jorge Odon, the inventor, and try the device on a simulator made available at the World Health Organization stand and during a private reception.

As in all previous presentations at scientific meetings, the Odon Device generated considerable positive interest. The FIGO Committee for Safe Motherhood and Newborn Health mentioned the Odon Device in its guidelines for the second stage of labour recently published in the *International Journal of Gynecology and Obstetrics*.

The Odon device is a new low cost instrument to deliver the foetus when complications occur.

See the FIGO Guidelines Here >>>>>

FIGO - Facilitating the Achievement of Universal Access to Reproductive Health

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 Organization (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 International Federation of Gynecology and Obstetrics (FIGO) is very much involved in both the areas of infertility and contraception. The FIGO 2012 World Congress staged two major occurrences: the presentation of 'The FIGO Fertility Tool Box'™ and the third edition of the 'Emergency Contraceptive Pills: Medical and Service Delivery Guidelines'.

"The emergency contraception guidelines were created by a group of experts working with the International Consortium for Emergency Contraception. The first release appeared in 2000, and the 2012 edition is endorsed by FIGO, whose representatives participated in reviewing the document," Professor Ian Fraser, Honorary Secretary of FIGO, explained.

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 midwives 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 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.

It consists of 6 components dealing with overcoming personal and societal barriers to infertility care, prevention, diagnosis, treatment, referral and resolution, plus the FIGO Fertility Daisy™. The Fertility Daisy™ deals with why one should care about infertility. "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. "Though the tool is intended primarily for women's healthcare providers, we hope it will also be used by policy makers," he added.

Professor Ian Fraser is one of the FIGO experts involved in the review of the emergency contraception guidelines. "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," he said.
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," he added.

Professor Ian Fraser also chairs the FIGO Working Group on Menstrual Disorders, which developed and released the "FIGO Classification of Causes of Abnormal Uterine Bleeding". "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," he concluded.

> **"It is hoped that The FIGO Fertility Tool Box™ 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 David Adamson, Reproductive Endocrinology and Infertility and Obstetrics and Gynecology**

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

"Preventable deaths occur in considerable numbers during pregnancy and childbirth in the developing world where maternal mortality ranges from 200 to 2,000 per 100,000 live births. Moreover, for each woman who dies, an estimated 16 to 30 survive avoidable complications, often miserably," said Professor Gamal Serour, President of the International Federation of Gynecology and Obstetrics (FIGO), presenting the most recent FIGO Initiatives for the prevention and treatment of post-partum haemorrhage and obstetric fistula in low-resource countries.

Post-partum haemorrhage (PPH) is the first cause of maternal mortality in low-resource countries, accounting for approximately 30% of maternal deaths, and is one of the most preventable. 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 refrigeration, 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.

"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, and are often abandoned by their husbands, forced to live in shame and social segregation," he continued.

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, medical and psychosocial care to women who have incurred fistulae.

The manual was produced with funding from the United Nations Population Fund (UNFPA), and with the collaboration of fistula surgeons and professional and specialist health organisations. It was pilot tested in several centres and is now being utilised for training in accredited centres.

FIGO is also involved in the provision of training workshops on PPH, Minimally Invasive Surgery (MIS), obstetric ultrasonography, basic surgical skills and pelvic floor dysfunction surgery - these are conducted in many African and Asian countries as the issues are highly relevant to maternal mortality and morbidity.

• 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 Organization, each year between 50,000 to 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.

Biolitec AG Presents New Laser Application for the Gentle Excision of Myomas

Biolitec AG presented its newest application at FIGO 2012. The worldwide leading specialist in medical laser technique presented HOLA™ (Hysteroscopic Outpatient Laser Applications) – the new minimally invasive method for the excision of myomas.

Myomas are often appearing benign tumours of the uterus, by which affects approximately every fourth or sixth woman of productive age in Europe. Even though myomas in some cases evoke no symptoms, heavy bleedings as well as pain and disturbance in function of organs can appear. Up to now, myomas are usually removed during a surgical or radiologic procedure.

The new HOLA™ therapy of Biolitec removes myomas of the uterus using minimally invasive techniques and with little side effects. A specially designed tip of the laser fiber enables contact vaporisation of the myoma tissue. The hysteroscopic vaporesection does not have any impact on the lining muscle and enables treatment of even bigger myomas. Interested parties were welcomed to familiarise themselves with the method during a workshop at the FIGO on October 10th and virtually test the application of HOLA™ with the simulator MyoSim.

For more information, please visit www.biolitec.de

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How to Accelerate Progress on Prevention and Care of Preterm Babies

Chaired by PMNCH Director Dr Carole Presern and obstetrician and epidemiologist Dr José Belizán, this FIGO 2012 session discussed key findings and next steps from Born Too Soon: The Global Action Report on Preterm Birth published in June 2012 – the first ever report providing country estimates of preterm birth around the world.

Since 2005 we have known that premature birth was the leading cause of neonatal deaths. Born Too Soon shows the extent to which preterm birth is on the rise in most countries, and is now the second leading cause of death globally for children under five, after pneumonia.

"We really have a problem on our hands here, and we don't have a lot in our armamentarium to deal with this," warned panelist Dr Joy Lawn, Director of Global Evidence and Policy with Save the Children's Saving Newborn Lives program and a key author on the report.

"The obstetrics community has a key role to play in reducing preterm births."

Dr. Joy Lawn,
Director of Global Evidence and Policy with Save the Children's Saving Newborn Lives program

Care all depends on where you're born, she explained; the gap between low- and high-income countries is less than 10 percent survival vs. more than 90 percent. Forty million births happen at home and of those 5.6 million are born preterm.

The good news is more than 70 percent of preterm babies could be saved without going to full intensive care. For instance, Kangaroo Mother Care – wrapping an infant to their mother's chest to prevent hypothermia – halves neonatal deaths for preterm babies < 2000 gm (comparative to incubator) at little to no cost.

"We must work with communities where preterm birth is still a burden," she said. "Your place of birth should not determine your right to life."

Carole Presern,
PMNCH Director

"We could save 450,000 babies every year," she said, except that not enough physicians are using this intervention."We think we have technology instead – but this can work with technology."

Birth spacing can also be scaled up. "And the converse is also true," said Dr Lawn. "There is excessive risk if interpregnancy interval is too long."

Adolescent pregnancies have a higher correlation with premature birth, still birth, low birth rate and asphyxia. "We recognise that being overweight or obese doubles risks as well," Dr Lawn added.

Aga Khan University's Professor Zulfiqar Bhutta, also speaking on the panel, said more focus is needed on women's education as a preterm birth prevention. "Forty-one percent of pregnancies are unplanned," he said, which is also a preterm risk factor.

In her closing remarks at the event, PMNCH Director Carole Presern stressed the role health workers must play to address these challenges and utilise proven interventions. "We must work with communities where preterm birth is still a burden," she said. "Your place of birth should not determine your right to life."

Every three years since FIGO's founding in 1954, thousands of gynecologists and obstetricians gather in one city to spend a week analysing and discussing new medical discoveries and looking at problems and issues that can be addressed by the application of low-cost techniques.

The site for the World Congress rotates between the Africa-Eastern Mediterranean, Asia-Oceania, Europe, Latin America and North America regions of FIGO. The site is selected six years in advance by a majority vote at the General Assembly.

FIGO 2012, hosted in the beautiful Italian capital Rome, was a resounding success, enjoyed by the many delegates in attendance.

Through the work of dedicated Committees and Working Groups, FIGO's work embraces many aspects of obstetrics and gynecology such as oncology, STDs/AIDS, perinatal health, education, safe motherhood, medical terminology, women physicians in the specialty, social activities on women's health, new technology, the pathology of the breast and ethics.

Whilst many successes were reported at the congress, President Professor Sir Sabaratnam Arulkumaran acknowledged there was much more work to do.

"On behalf of FIGO, I would like to thank the world of obstetricians and gynecologists, national governments and our professional partners and donors (which include ICM, ICN, IPA, Bill & Melinda Gates, The Fistula Foundation, USAID, UNFPA, WHO, Jhpiego, IPAS etc among others) for an incredible job well done in terms of Millennium Development Goal 5.

I would also like to put on record the excellent work done by the FIGO Officers, Executive Board and staff over the last three years under the esteemed leadership of Professor Gamal Serour."

FIGO President
Prof. Sir Sabaratnam Arulkumaran

XXI World Congress The International Federation of Gynecology and Obstetrics (FIGO) 2015

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We look forward to seeing you in Vancouver for FIGO 2015!

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Image Guided Adaptive Brachytherapy in Locally Advanced Cervical Cancers: Preliminary Results and Perspectives

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Introduction

Radiation therapy (external beam radiotherapy, EBRT, followed by brachytherapy) is the cornerstone of the treatment of locally advanced cervical cancer.[1] Brachytherapy plays a fundamental role in the treatment of locally advanced cervical cancers. It permits delivery of high doses to the tumour while minimising the doses delivered to organs at risk (rectum, bladder, sigmoid colon and small bowel). In typical schedules, 40 to 50% of the total dose delivered to the high-risk clinical target volume (HR-CTV) is delivered by brachytherapy. Another advantage over external beam radiotherapy is to eliminate organ motion, as the radioactive sources follow the tumour.[2] In combination with radiotherapy it is a standard of care for tumours staged from IB2 to IVA according to The International Federation of Gynecology and Obstetrics (FIGO).

Over the past 15 years, two major advances have taken place in this strategy. The first was concomitant chemotherapy, which became standard in 1999, after the publication of 5 randomised studies showing its superiority over exclusive radiotherapy.[3-7] A recent meta-analysis revealed an improvement of 6% for loco-regional disease in locally advanced cervical carcinoma, which translated into a gain of 5% in overall survival.[8] Secondly, technical advances in the field of brachytherapy allowed the use of 3D modality images, such as MRI or CT. So far, conventional brachytherapy was based on geometrically constructed prescription points (A points) and on the use of orthogonal X-rays for planning. Standard prescriptions were used regardless of tumour size, shape, or response to EBRT. In the same way, doses delivered to OAR (bladder and rectum) were evaluated by calculating dose delivered to precise points.[9] It was shown that those two ICRU (International Commission for Radiation Units and Measurements) points are generally underestimating the maximal delivered dose compared to 3D evaluated dose assessment. Kang *et al*. studied the efficacy of such standard plannifing to point A by delineating gross tumour volume (GTV) on CT-scans. They showed that prescribing to point A overestimates the dose delivered to the tumour.[10] By generating dose volume histograms, they reported that the prescribed dose to point A encompassed 98.5%, 89.5%, 79.5 and 59.5% of the (GTV) on average, for staged IB1, IB2, IIB and IIIB lesions respectively, and therefore demonstrated the limitations of such a technique.

The integration of 3D images into treatment planning, allowed delineation of tumours and OAR, making the use of points obsolete. Wachter *et al*. showed that dose volume histograms generated from outer organ contouring were a good estimation of doses given to organ walls, when considering small volumes such as 0.1 cm^3 or 2 cm^3.[11]

The GEC-ESTRO group (Groupe Européen de Curiethérapie- European Society for Therapeutic Radiology and Oncology) published recommendations in 2005 and 2006, on tumour and OAR contouring, and on reporting dose volume parameters.[12, 13] They proposed an individual approach, by defining two target volumes at the time of brachytherapy: a high risk CTV encompassing the residual tumour after EBRT as well as grey zones and at least the whole cervix and an intermediate risk CTV (IR-CTV), taking into account the initial tumour volume as well as the residual volume at the time of brachytherapy. These recent concepts defined image guided adaptive brachytherapy, which implies therefore: 3D imaging and dose optimisation to target volumes.

Currently, dose constraints to the maximal 2 cm^3 of the OAR relies on the experience of conventional X rays based brachytherapy: 70-75 Gy (Eq D2, with a α/β of 3 for late morbidity and a repair half-time of 1.5 hours) for rectum, 85-80 Gy for bladder, and by analogy to rectum, at the lack of data, 70-75 Gy for sigmoid.[14] No reliable dose constraints could be established for small bowel or vagina.

Preliminary Results

Following its publication in 2005 and 2006, the GEC-ESTRO recommendations became a standard to guide and report brachytherapy. IGABT was rapidly implemented throughout Europe. In a descriptive survey, Guedea *et al*. reported an increase in the use of CT based dosimetry from centres around Europe, from 33% in 2001 to 61% in 2010.[15]

Several dosimetric studies show a clear advantage to using IGABT in the treatment of locally advanced cervical cancer over conventional 2D brachytherapy.[16, 17] Tanderup *et al*. reported comparisons of 2D standard plans to MRI based plans in 72 patients. For small tumours, HR CTV was well covered in 94% of the cases with standard plans, but OAR tolerance

thresholds were exceeded in 72% of the cases (maximal 2 cm^3 of bladder < 90 Gy and 2 cm3 of the rectum/sigmoid < 75 Gy.[18] Optimisation permitted to lower this rate to 6%. For larger tumours, standard plans were adequate in only 25% of the cases whereas full coverage could be obtained in 72% of the cases with optimisation. Zwahlen *et al*. reached the same conclusion with a smaller set of patients (20).[19]

Dimopoulos *et al*. showed that MRI enables accurate delineation for GTV, HR-CTV, IR-CTV and OAR. Therefore, MRI has been considered as the reference imaging for contouring GTV and CTVs. However, Viswanathan *et al*. compared MRI and to CT in a dosimetric study. In this publication, ten patients underwent both CT and MRI after brachytherapy. Contouring and planning was according to the GEC-ESTRO recommendations. They concluded that there was no difference in delineating OAR but CT systematically overestimated the tumour volumes for defining HR and IR CTVs.[20]

The first clinical series came from Potter *et al*. They reported the outcomes of 145 patients treated with high-dose rate brachytherapy among two periods: 1998-2000, during which MRI was used, but limited optimisation was performed and 2001-2003, during which they applied the GEC-ESTRO recommendations and the concepts of risk volumes (HR and IR-CTVs).[21] Outcomes were similar for small tumours, but authors showed an improvement of nearly 20% in local control (from 64 to 82%) in the group a tumours > 5 cm in width, and 30% in overall survival (from 28 to 58%) combined with a reduction of severe toxicities (from 10 to 2%). From the same series of patients, Dimopoulos *et al*. showed a dose effect relationship between dose to the HR-CTV and local control. Patients who achieved D90 (dose delivered to 90% of HR-CTV) > 87 Gy (2 Gy equivalent) had a local relapse rate of 4%, whereas those who had a D90 < 87 Gy had a 20% risk of local relapse.[22]

Recently, Schmid *et al*. reviewed the data of 265 patients treated from 1998 to 2010. They reported a correlation between dose coverage and local relapse. The D90 was 77 Gy for patient who experienced local relapse whereas it was 95 Gy for those with local control.[23] In 85% of the relapses, low dose regions (<87%) could be identified. In a recent update of the Vienna series, Potter *et al*. published an update of their series.[24] One hundred and fifty six consecutive patients treated from 2001 to 2008 were reported. Local control was 98% for tumours 2-5 cm width, and 95% for larger tumours. Late treatment induced toxicity was low, as only 11 grade 3-4 events were reported for the whole series. Georg *et al*. published correlations between DVH parameter and morbidity. They showed that the D2 cm^3 had a good predictive value for late rectal and bladder toxicities.[25] They failed to find correlation for sigmoid and bowel, possibly due to a lack of events.

In our institution, we published the first series on MRI based pulsed-dose rate brachytherapy, in 45 patients with no local recurrences after a median follow-up of 2 years.[26] We recently updated our database.[27] Local control was 92% in a series of 163 patients with a median follow-up of 37 months. According to the CTC 3.0, 7.4% of the patients experienced late grade 3-4 toxicity, but most of those had undergone post radiation hysterectomy: 14.8% versus 2.9% (p=0.005). At the beginning of our experience, post radiation hysterectomy was still part of the treatment for stage I and II lesions, but the efficacy of IGABT on local control led us to abandon this procedure which was shown to cause unacceptable morbidity, particularly when the rate of complete histological response to IGABT was taken into account.[28] In a smaller set of patients with advanced disease (mainly stage III and IV), Mahantshetty *et al*. reported promising results in a small cohort of 24 patients from which half had stage IIIB diseases. Only one local relapse was reported after 24 months of follow-up.[29]

Recently, a French multicentric prospective non randomised study comparing 2D versus 3D brachytherapy was published. Patients were divided into 3 groups: brachytherapy followed by surgery for IB1 lesions (group 1), chemoradiation followed by brachytherapy and surgery (group 2) or definitive radiation therapy (chemoradiation followed by brachytherapy, group 3) for locally advanced staged lesions.[30] In each group, patients were treated either with conventional 2D brachytherapy or 3D image guided brachytherapy following the GEC-ESTRO recommendations, according to availability of equipment and at the discretion of local investigator. Results showed significantly better outcomes in the patients treated with 3D brachytherapy in comparison to 2D brachytherapy in terms of local relapse free survival (78.5% versus 73.9% in group 3 and 93% versus 84.7%, in group 2, p=0,003). This was translated into a significant improvement by 4-5% of disease free survival in groups 2 and 3, without any significant impact on overall survival. Authors also showed an improvement of grade 2-4 toxicities: 42.4% versus 53.5% in group 3 and 29.4% versus 40.6% in group 2 (p=0.028). In a separate publication the investigators reported a correlation between D0.1 cm^3, D2 cm^3 of the rectum and D0.1 cm^3 and dose delivered to the ICRU point of the bladder and grade 2-4 toxicity.[31] It should be noted that 57% of the patients of the series had a post radiation hysterectomy.

Perspectives

Preliminary reports are encouraging, but the next step is to provide higher scientific evidence of the efficacy of IGABT. The GEC-ESTRO network is leading a prospective non randomised multicentric study, EMBRACE, on MRI based IGABT.[32] Twenty four centres around the world are attending the study. The aim is to include 1,000 patients. Accrual begun in 2008 and should close in late 2013. The principal objectives are local control and morbidity. One other major purpose of this study is to establish DVH correlations with outcome, both for CTVs and OAR. Dose constraints in both favourable and unfavourable cases would permit to stratify diseases and decide to escalate the dose or conversely to de-escalate the dose in good responders.

At the same time, the network created a wide database of patients treated before the launch of EMBRACE, named retroEMBRACE.[33]

Preliminary results presented in abstract form seem to confirm the promising results published by individual centres.[34]

Another poorly understood aspect of morbidity after treatment for cervical cancer is sexual morbidity. Most patients complain of dyspareunia which is multi factorial: post radiation vaginal sequelae, tumour related changes, psychological consequences, personal culture and treatment induced menopause. GEC-ESTRO has just launched an ancillary study of this subject in order to accurately report morbidity and quality of life, and to correlate doses delivered to different regions / points of the vagina with radiation induced vaginal toxicity.

Image guided adaptive brachytherapy appears highly effective, improving local control with acceptable morbidity. As a consequence, the pattern of relapse is changing, with the emerging significance of distant relapses. In our series, distant metastasis is the first site of relapse in more than 70% of the patients who relapse.[28] Furthermore, in half of the cases, distant metastasis is isolated. This clearly raises the question of more aggressive systemic treatment. Concomitant chemoradiation was shown to have little but significant impact on distant control. Other chemotherapies have been studied such as gemcitabine which is a powerful radiosensitiser, and seems to be effective in combination with cisplatinum.[35] In our institution, we are completing a phase I study on cidofovir, an anti-HPV drug which was showed to be a radiosensitiser, in combination with concomitant chemoradiation.[36] Notably, a phase III study, OUTBACK, has been launched in high risk patients (stage III or IV or lymph node positive), evaluating the role of adjuvant carboplatin-paclitaxel.[37]

Conclusion

Since the late 1990s, significant advances have been made in image guided adaptive brachytherapy for locally advanced cervical cancer. The GEC-ESTRO recommendations helped to standardise and disseminate the technique. Initial clinical results showed that local control in bulky tumours could be improved by 20%, with an acceptable morbidity. The international collaborative study EMBRACE is hoped to definitively establish MRI based brachytherapy as a treatment gold standard.

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Targeting Elements of the Epithelial Growth Factor Receptor Pathway in Persistent and Recurrent Cancers of the Uterine Cervix

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Introduction

Worldwide, cervical cancer is the third most commonly diagnosed cancer and the fourth leading cause of cancer deaths in women.[1] Although the incidence in the US has been decreasing over the past two decades secondary to the availability of effective screening programs, cervical cancer remains an important public health concern.[2] In 2010, the American Cancer Society estimated that 12,200 women would be diagnosed with cervical cancer and 4,210 women would die from their disease.[3] Early stage cervical cancers can be treated successfully, and with equal efficacy, using either radical surgery or radiation.[4] However, approximately 25% of women have advanced disease at diagnosis, and the overall survival for these patients is low, even with multimodality therapies.[5] Furthermore, despite improvements in treatment, up to 35% of women will eventually develop persistent, recurrent or metastatic cervical cancers which will respond only briefly to platinum-based chemotherapy.[6,7]

Historically, radiation was the mainstay of treatment for locally-advanced cervical cancer.[8] In 1999, five large clinical trials from the Gynaecologic Oncology Group (GOG), Southwest Oncology Group and Radiation Therapy Oncology Group, encompassing more than 1,800 patients, published remarkably consistent data which changed the landscape of treatment of cervical cancer.[9-11] These trials each demonstrated a reduction in relative risk of death of 30-50% with the addition of concurrent cisplatin chemotherapy as a radiosensitiser.[9] These data led the NCI to endorse platinum-based chemotherapy for the treatment of locally advanced cervical cancer. Since that time, single-agent cisplatin with radiation has been the mainstay of treatment, and it continues to be regarded as the most active chemotherapeutic agent in cervical cancer.[7,8,11] More recently, the GOG has conducted several trials aimed at the identification of other single or multi-agent radiosensitiser regimens that demonstrate improved response and overall survival rates while maintaining satisfactory quality of life.[9,10]

Recurrent cervical cancer usually cannot be cured, particularly when surgical resection is not feasible and radiation salvage is not possible secondary to previous treatment, or when patient performance status is low.[8] Thus, the goal for these patients is palliation of symptoms while preserving quality of life; systemic chemotherapy remains the mainstay of therapy.[7,8,12,13] In the early 1980s, cisplatin was first investigated for the treatment of advanced and recurrent cervical cancers with a reported response rate of 38%.[12] Overall survival using cisplatin in this setting was demonstrated to be 7 months.[7] Since that time, various agents have been evaluated for response in the setting of recurrent or advanced disease,[7,13] and of the 21 demonstrating efficacy with response rates of at least 15%, the five yielding the greatest activity include cisplatin, paclitaxel, topotecan, vinorelbine, and ifosfamide.[12]

Combination chemotherapy regimens studied by the GOG in hopes of capturing the effects of single agent additive or synergistic activities while distributing drug toxicities.[7,13] Despite multiple studies investigating the efficacies of combined regimens of agents with known activity against recurrent cervical cancer, only one GOG protocol (GOG 179) demonstrated an improvement in overall survival. The cisplatin plus topotecan arm enjoyed improved median overall survival (9.4 months vs. 6.5 months),

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median progression free survival (4.6 months vs. 2.9 months), and response rates (27% vs. 13%) when compared to the cisplatin single-agent arm.[14] In 2006, following the results of GOG protocol 179, the combination of cisplatin plus topotecan was FDA-approved for the first-line treatment of recurrent cervical cancer.[7,8,13,14] Other investigations, intent on improving patient tolerance and quality of life measures, have explored the use of carboplatin and paclitaxel in the recurrent cervical cancer setting with promising results, though randomised head-to-head trials are lacking.[8]

In an effort to further improve treatment efficacy, several studies have assessed the effect of adding additional cytotoxic agents to the cisplatin-containing doublets; however, none of these so-called triplets have shown improvement over cisplatin-based mono- or doublet therapy.[7,12] Given the limitations of effective traditional chemotherapy regimens for advanced and recurrent cervical cancer, focus has necessarily moved to the new frontier of biologic therapy.[15]

The Premise of Targeted Drug Therapy

Targeted molecular therapies comprise this newest frontier of oncology research.[16-21] Recent investigation has concentrated on the development of novel treatments designed to interrupt cellular pathways crucial to oncogenesis, and in fact, these medications represent a large proportion of drugs undergoing evaluation in current and new clinical trials.[17] Identification of the intracellular signals responsible for conferring malignant potential on tumour cells enables therapeutic discrimination between malignant and healthy cells.[16,17] The expectation is that targeted therapies, in contrast to traditional chemotherapeutic agents, will provide enhanced patient outcomes and improved efficacy in the setting of superior, or at least complementary, toxicity profiles.[18,22] Furthermore, targeted drugs provide alternative approaches to disruption of carcinogenesis which may prove to be synergistic with conventional cancer therapies.[22] While the advent of innovative treatment modalities for cancers has improved the landscape for affected patients, the overall response to therapy thus far has been modest.[20,21,23]

Epidermal Growth Factor Receptor (EGFR)

Nonmalignant cells develop in a regulated fashion using a series of intracellular signaling pathways which dictate typical cellular responses such as angiogenesis, proliferation, and cell survival. Preferential activation of these pathways leads to promotion of tumour growth, invasion, and metastasis. Receptor tyrosine kinase activation mediates multiple intracellular signaling pathways, and dysregulation of the activation and expression of the components of this pathway is considered one etiology of tumourogenesis.[18,23,24] The EGFR is the gatekeeper of one such critical tyrosine kinase cascade, and as such, exemplifies a target for novel chemotherapeutics.

EGFR, a member of the receptor tyrosine kinase (RTK) family erbB-1 or HER1, is a 170kDa transmembrane protein which serves to regulate a variety of downstream signals influencing tumourogenesis.[17,22,24] The receptor is composed of an extracellular ligand-binding region, a transmembrane region, and an intracellular tyrosine kinase domain which mediates intracellular signaling through the activation of cytoplasmic messengers. Following binding of the natural ligands (i.e., transforming growth factor alpha [TGF-α] and EGF), the extracellular portion undergoes conformational change to facilitate homo- or heterodimerisation with nearby EGFR or EGFR-related receptors.[22,24] The dimerisation promotes activation of the tyrosine kinase domain and initiation of the intracellular signaling cascade, as well as prompting internalisation of the receptor for eventual degradation or recycling.[18,22,24] Intracellular messengers recruit transcription factors in the nucleus and activate specified genes.[22]

Downstream pathways activated by the ligand-binding cascade include those influencing apoptosis, proliferation, angiogenesis, metastasis, invasion, and survival. The EGFR is constitutively expressed in many normal epithelia, including in skin and hair follicles. In the skin in particular, EGFR plays a critical role in the maintenance of epithelial integrity.[25] In contrast to nonmalignant tissue, several epithelial cancers, including tumours of the colon, head and neck, breast, lung, kidney, bladder, brain and pancreas, demonstrate overexpression of EGFR, albeit at varying rates.[16-18,24] Overexpression of EGFR within malignant tissues has been associated with more aggressive disease and a poorer prognosis, as well as resistance to cytotoxic agents and impaired treatment responsiveness.[2,5,6,9,15,22,26-31]

Monoclonal Antibodies

There are two main strategies for achieving EGFR pathway disruption: by employing either tumour-specific monoclonal antibodies or by treating with small-molecule tyrosine kinase inhibitors.[19,22,32] Monoclonal antibodies leverage the immune system for enhanced tumour specificity, acting upon tumour antigens ideally having lesser expression in healthy tissue. Cetuximab/C225 is a recombinant, human-murine chimeric monoclonal IgG1 antibody which binds the EGFR with a 2-log higher affinity than native ligands such as TGF-α and EGF.[16-18,24] Following binding of the antibody to the extracellular domain, the complex is internalised for eventual degradation.[33] Unlike the effects of ligand-binding, the binding of cetuximab does not stimulate tyrosine kinase activity, and the dependent intracellular pathways remain quiescent.[33] This process also results in impaired recycling of receptors to the cell surface, leading to overall receptor downregulation.[16,17,24,33] Recent studies have demonstrated a tyrosine kinase-independent, antibody-induced localisation of the EGFR to the nucleus following endocytosis.[33] A small fraction of receptors are transported to the nucleus via the endoplasmic reticulum, though what influence this translocation has on the biologic activity of cetuximab is unknown.[33]

In general, cetuximab mediates its action through the inhibition of tumour proliferation, angiogenesis and metastasis, induction of

apoptosis, and/or promotion of cell cycle arrest.[16,24,33] It also serves as a radiosensitiser when used concurrently to traditional chemotherapeutic agents. Cetuximab promotes cell cycle arrest in the G1 phase which culminates in cellular apoptosis and leads to overall inhibition of tumour proliferation.[24] In a separate signaling cascade, angiogenesis is interrupted by the inhibited production of angiogenic factors including VEGF.[24] This antiangiogenic activity mediates a decrease in microvessel density of the tumour while advancing endothelial cell apoptosis.[18] Cetuximab may also prevent nuclear transport of EGFR, thereby inhibiting DNA repair mechanisms that address chemo- or radiotherapeutic-induced DNA damage.[24,34] Finally, cetuximab likely participates in antibody-dependent cell-mediated cytotoxicity secondary to its immunoglobulin G1 structure.[20]

Reported toxicities associated with cetuximab include constitutional symptoms such as fevers, chills, fatigue and nausea, infusion reactions, and hypersensitivity reactions, as well as an acneiform skin rash, reported in some studies to be up to 88% of patients.[18] Severity of the rash has been linked in several studies to improved efficacy and therapeutic response.[17] However, cetuximab is overall well-tolerated. In Phase I studies regarding the immunogenicity of cetuximab, less than 4% of patients developed human antichimeric antibodies (HACAs) following administration of the medication.[16,24]

Panitumumab is a fully human IgG2 monoclonal antibody to EGFR which was FDA-approved for the treatment of metastatic colorectal cancer.[16,18] Similar to cetuximab, high-affinity binding of panitumumab to the EGFR occurs and this interaction inhibits EGF-dependent intracellular pathways.[18] Like its relative cetuximab, panitumumab arrests the cell cycle at the G0/G1 interphase, and it has also been shown via xenograft models to have activity in a variety of solid tumours.[18] Observed adverse events to this therapy include pulmonary fibrosis, rash, infusion reaction, hypomagnesemia, nausea and constipation.[16] In 2006, the FDA approved panitumumab for the treatment of some colorectal cancers.[23] To date, no data have been reported on its effect in clinical trials for cervical cancer.[18]

Matuzumab is a humanised IgG1 monoclonal antibody also targeting the EGFR. The high-affinity binding to the receptor inhibits downstream pathway mediators in a comparable manner to cetuximab and panitumumab.[18] Xenograft models have demonstrated antitumour activity, and tumour responses have been documented in several solid tumours, including cervical.[18,35,36] Additional monoclonal antibodies to the EGFR have been developed and are in various stages of the clinical investigations preceding FDA approval,[19] while still others with fluctuating properties such as epitope, affinity, and isotype continue to be discovered.[21,32]

Small-molecule Tyrosine Kinase Inhibitors

Small-molecule tyrosine kinase inhibitors (TKIs) target the EGFR pathway through direct blockade of the intracellular tyrosine kinase, rather than through indirect inhibition through interaction with the receptor. Three small molecule TKIs are in clinical use today erlotinib, gefitnib, and lapatinib.[19,22] Each is based on a 4-anilinoquinazoline core scaffold which reversibly inhibits the EGFR while competing with ATP in the intracellular tyrosine kinase domain.[19,22] As the TKIs provide blockade of the EGFR downstream mediators, it is not surprising that the toxicity profiles are similar to those seen with the monoclonal antibody therapies.[22] Typical side effects include diarrhoea and rash. As TKIs have the advantage of oral administration, the possibility of more convenient dosing necessarily aroused enthusiasm in early clinical trials.

EGFR and Cervical Cancer

The precise role of EGFR in cervical cancer has been an ongoing investigation.[5,26] While early studies demonstrated overexpression in cervical cancers and cervical intraepithelial neoplasia similar to that found in other solid tumours, later research provided less convincing data, noting only a small percentage of differential expression of EGFR in malignant vs. healthy cervical epithelium.[5] In fact, the reported range of EGFR overexpression in cervical cancers is wide: 6-85%,[6,9,15] and microarray analysis of 23 human cervical cancer cell lines confirmed wide variation in levels of expression of EGFR, suggesting likely differential sensitivity of these tumours to cetuximab therapy.[6] Newer data also suggests that immunohistochemical analysis may not capture EGFR expression consistently, and could account for the wide variation in expression levels seen in previous studies.[5] Despite early contradictory results, more recent studies confirm EGFR overexpression as a poor prognostic indicator in cervical cancers, similar to data reviewed earlier regarding other tumours.[2,6,9,15,26] Bellone *et al*. tested EGFR expression in both primary and established cervical cancer cell lines, and repeatedly demonstrated higher levels of EGFR expression in the recurrent or metastatic cell lines in contrast to primary sites. This differential expression suggests a role for biologic targeting of cervical cancers in the recurrent or metastatic setting where effective salvage therapies are lacking.[6] Furthermore, the reported activity of cetuximab in metastatic colorectal cancers,[18,25] and more importantly, its efficacy in the histologically similar squamous cell carcinomas of the head and neck[34] provided the foundation rationale for its use in cervical cancer. In particular, infection with high-risk HPV genotypes has been implicated in the development of at least 25% of squamous cell carcinomas of the head and neck[37,38] as well as the majority of cervical cancers.[5]

Cetuximab and Cervical Cancer

Early *in vitro* studies of cervical cancers with cetuximab revealed exquisite sensitivity of these tumours to monoclonal antibody therapy.[6] Based on the known efficacy of cisplatin and topotecan for advanced cervical cancer, and the promising results observed for Cetuximab in the treatment of colon and head and neck squamous cell carcinoma, a Phase II trial was designed to investigate the efficacy of the

combination regimen with the addition of cetuximab. The chemotherapeutic regimen evaluated included cisplatin 50 mg/m^2 on day one plus topotecan 0.75 mg/m^2/day from days one to three every three weeks combined with cetuximab (initial dose of 400 mg/m^2 followed by subsequent weekly dose of 250 mg/m^2). Nineteen of the planned 44 patients were enrolled prior to premature closure of the study due to higher than expected severe toxicities.[2]

Only two (11%) patients completed the planned six cycles of chemotherapy. Treatment was stopped for three (17%) patients secondary to disease progression and six (33%) for toxicity. Out of the 18 patients who received study treatment (one enrolled patient never started therapy), thirteen had to be hospitalised for toxicity events, with a median duration of 7.8 days hospitalisation.[2] Five (28%) patients died during treatment: two patients died from sepsis in the setting of grade 4 neutropaenia and thrombocytopaenia. These deaths were clearly attributable to the treatment. One patient died from pulmonary embolism with relationship to treatment considered as "possible", and another patient died from acute respiratory distress syndrome related to an inhalation pneumopathy that was considered not study-related.

Grades 3 and 4 neutropaenia occurred in 72% of patients, while grades 3–5 infection and febrile neutropaenia occurred in 39% and 28% of patients, respectively.[2] Grades 3 and 4 thrombocytopaenia occurred in 61% of patients. Two (11%) patients had grades 3 or 4 renal toxicity and two (11%) patients experienced pulmonary embolism. Grade 3 skin reactions were observed in four (22%) patients. The severe haematologic toxicities notwithstanding, an overall response rate of 32% was demonstrated despite the abbreviated study interval, indicating significant activity of the cetuximab-containing regimen.[2] The median PFS and OS observed were 5.7 and 7.3 months, respectively.[2]

More recently, Hertlein *et al.*[39] published a retrospective study of five patients with advanced cervical cancer treated with cetuximab monotherapy as third- to fifth-line therapy. One of the five patients exhibited stable disease during the therapy, while the remaining four patients progressed. Median survival from the initiation of the cetuximab therapy was 8.6 months. The treatment was well-tolerated, with side effects including the acneiform rash (four of the five patients), fatigue, headache, and nail changes. The authors concluded that, in this small, heavily pre-treated population, no benefit was observed from the addition cetuximab monotherapy.[39] Further, prospective, randomised studies will be needed in order to extrapolate from this conclusion.

Several Gynaecologic Oncology Group studies, regarding the use of cetuximab for the treatment of cervical cancers are ongoing, including: a study of the efficacy of single agent cetuximab in recurrent cervical cancer, a Phase I trial of tailored radiation therapy with concomitant cetuximab and cisplatin as radio-sensitisers in primary cervical cancer, as well as a Phase II trial comparing cetuximab combined with cisplatin for recurrent or persistent cervical cancers.[15] Recently published data from the Phase II trial evaluating the addition of cetuximab to cisplatin for the treatment of advanced, recurrent and previously treated cancers of the cervix (GOG 0076DD) reveals that the combination regimen is well-tolerated, with minimal toxicity.[40] Seventy-six patients were entered onto the study. Of these, 69 were eligible and evaluable. Fifty-six (81%) patients received prior radiation, while forty (58%) patients previously received chemotherapy (CT). There were eight (17.2%) responses with an observed 25% progression free survival (PFS) at six months.[44] Assessment of EGFR in the tumours of enrolled patients confirmed immunohistochemical overexpression of EGFR protein in this malignancy; indeed, EGFR was expressed in 98% of tumours analysed.[40] Of the 48 tumours analysed, 25 (52%) had EGFR expression in greater than 81% of cells (high percent positive). Notably, an increased EGFR expression was not associated with age, performance status, number of prior regimens, or having tumour response or stable disease. Furthermore, higher levels of EGFR overexpression conferred worse prognosis in terms of increased likelihood of disease progression at six months as well as decreased responsiveness to cetuximab. Pre-treatment EGFR expression in greater than 81% of cells however, was associated with a two-fold higher risk of progression (hazard ratio [HR] =1.99, 95% confidence interval [CI] =1.08-3.68), but not overall survival (HR=1.37, 95% CI=0.72-2.61).[40] The combination of cisplatin and cetuximab therapy demonstrated rates of disease stabilisation and clinical objective response comparable to the agents with highest activity in the recurrent setting.

Small-molecule TKIs and Cervical Cancer

Initial *in vitro* studies of erlotinib were provocative: administration of this TKI reduced EGFR autophosphorylation in mice by over 70% in 24 hours. An early Phase I trial of erlotinib in combination with cisplatin and radiation in advanced cervical cancers confirmed a tolerable dosing scheduled and it suggested the addition of the TKI may be effective, with a demonstrated complete response in over 90% of the patients.[41] Unfortunately, the trials which ensued have been disappointing.[42-44]

Armed with the demonstrated efficacy of erlotinib in Phase III trials in non-small cell lung cancer (NSCLC) and pancreatic cancers, the GOG elected to perform a Phase II multi-center, single-arm investigation of the efficacy and toxicity as a second- or third-line agent in recurrent or persistent cervical cancers (GOG 227D).[42] The treatment was comprised of daily erlotinib (150 mg) until disease progression or unacceptable toxicity. Of the 25 evaluable patients, there were no objective responses and 16 patients experienced stable disease. A single patient remained progression-free at six months, precluding initiation of a second stage of the trial as a minimally significant proportion (25%) was not achieved.[42] Median PFS was 1.87 months while median OS was 4.96 months.[42] A median of two 28-day cycles were administered. Toxicities included Grade 3 diarrhoea, nausea, emesis, dehydration, and anorexia, one case of anaemia, and one

Grade 4 renal toxicity which was ultimately reversed. Several patients experienced a mild rash, and for two patients the dermatologic effects were Grade 3.[42] Despite the drawbacks inherent in a Phase II study, the lack of demonstrated efficacy suggests that proceeding to a Phase III trial would be fruitless.

Similar negative results exist for the other TKIs. In 2008, Goncalves *et al*.[43] reported on a Phase II trial evaluating gefitinib as second- or third-line treatment in advanced or recurrent cervical cancers. In this multicentre, single-arm study, patients were treated with daily, oral gefitinib 500mg until disease progression or unacceptable toxicity. Of the twenty-eight patients evaluable, there were no objective responses, six patients with stable disease, and the majority (73.3%) had progression.[43] Median time to progression was 37 days, and median OS was 107 days.[43] Biopsies taken prior to the initiation of the study therapy confirmed EGFR expression in this malignancy, with high levels noted in the majority of patients (86.7%). The toxicity profile of this drug was similar to that seen in the GOG study of erlotinib, and overall, the therapy was well-tolerated. Again, the trial failed to meet its primary objectives, and the authors concluded that gefitinib likely has negligible activity in cervical cancer.

Monk *et al.*[44] recently reported on a randomised Phase II, comparative trial evaluating two TKIs in mono- and in combination therapy in advanced and recurrent cervical cancers following at least one prior chemotherapy regimen. The trial was composed of three arms: the antiangiogenesis agent pazopanib alone, the dual EGFR/HER2 agent lapatinib alone, and both agents in combination. As with the preceding two trials, drug efficacy and toxicity were assessed until progression or unacceptable toxicity. At interim analysis, the combination therapy arm was abandoned secondary to both imbalanced toxicities and futility. While pazopanib therapy had demonstrated a confirmed response in seven patients, the lapatinib arm resulted in a response in four patients. Furthermore, lapatinib therapy resulted in a shorter PFS and shorter OS.[44] The toxicity profiles revealed that both agents were tolerated well. This investigation, while perhaps highlighting pazopanib as a target for further investigations, yet again confirms discouraging results with an anti-EGFR TKI.

Resistance to EGFR-modulation

While modulation of EGFR by targeted therapies such as cetuximab has demonstrated efficacy against various cancers in Phase I/II trials, a subset of patients with these diseases have reduced initial responsiveness to the therapy, and others subsequently develop therapeutic resistance.[19,21,23] Furthermore, several investigators have demonstrated that density of EGFR expression in tissue does not correlate with response to anti-EGFR therapy.[25] Several potential etiologies of the decreased efficacy of anti-EGFR therapy exist, including somatic mutations of the EGFR, circumvention of the EGFR by preferential activation of neighboring tyrosine kinase receptors, and EGFR-independent activation of intracellular signaling intermediaries such as KRAS, BRAF and others.[19,21,23] In fact, mutations of the KRAS oncogene have been identified in 15-30% of patients with NSCLCs and 40-45% of patients with colorectal cancers. These mutations result in constitutive activation of the KRAS-dependent pathway independent of EGFR blockade, and necessarily confer resistance to cetuximab.[18,19,21,23]

Conclusion

In the setting of advanced and recurrent cervical cancers, traditional therapies with the best efficacy still provide response rates of only 17-38%. The search for novel therapeutics to address this relative lack of efficacy is ongoing, particularly in the realm of targeted drug therapy, with its rational mechanisms of action and complementary toxicities. While targeted monoclonal antibody therapy has shown some efficacy in this malignancy, the small-molecule TKIs have had repeatedly disappointing results. The combination of cetuximab with cisplatin is adequately tolerated and appears to increase progression free survival beyond cisplatin therapy. Patients however, with high EGFR expression status are less likely to remain progression free of disease at six months. Stratification of patients based upon EGFR status may select a group for which this regimen is most effective.

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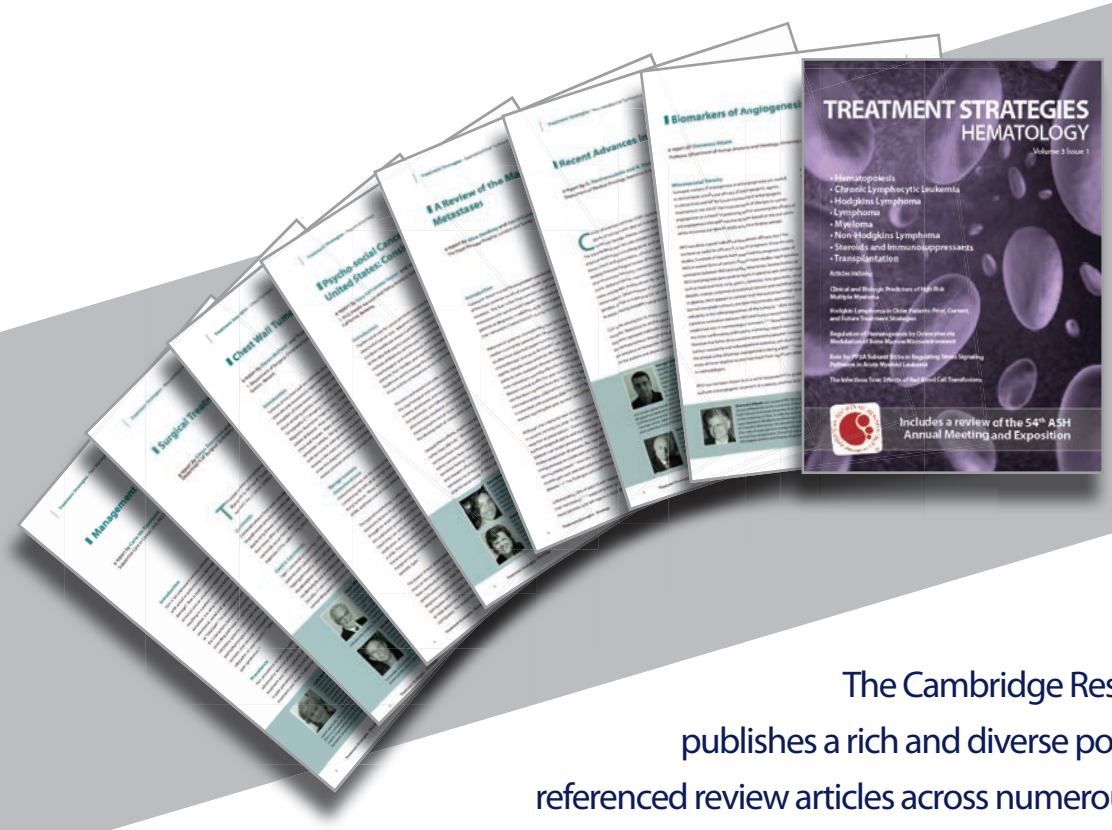

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Adjuvant Treatment Paradigms in Endometrial Adenocarcinoma

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Introduction

Endometrial adenocarcinoma is the most common gynaecologic malignancy in the United States, affecting over 47,000 women annually and causing approximately 8,000 deaths each year.[1] It is also a significant problem in Europe and parts of South America, but less so in Asia and Africa. The incidence of endometrial cancer rises dramatically between the ages of 40-60, and occurs more often in whites than non-whites. Well established risk factors for the development of endometrial cancer include nulliparity, unopposed exogenous estrogen use, tamoxifen exposure, and obesity. Higher parity, smoking, and use of combined oral contraceptive pills are known to decrease risk.[2] Genetic factors contribute to only about 10% of endometrial cancers, mostly due to hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome, and to a lesser degree, Cowden syndrome; both of these genetic conditions follow autosomal dominant inheritance patterns.

Endometrial adenocarcinoma is broadly categorised into two types based on clinical and pathologic factors.[3] Type I endometrial carcinomas follow an estrogen dependent pathway whereby tumours progress along a continuum from a precursor lesion of atypical hyperplasia. These tumours comprise the majority of endometrial cancers and typically affect younger women, are limited to the uterus, are endometrioid histology, and overall have a favourable prognosis.

In contrast, type II carcinomas appear to develop independently from any estrogen exposure. They occur more frequently in an older population, disproportionately affect African Americans, and are seen with atrophic, as opposed to hyperplastic, endometrium. In general, Type II endometrial cancers are comprised of serous and clear cell histologies. However, there is debate as to whether grade 3 endometrioid carcinomas should also be included in this category. Type II tumours are more frequently diagnosed at an advanced stage and confer a worse overall prognosis compared to type I carcinomas, even in early stages.

From a molecular perspective, the two types also delineate along different pathways, with type I tumours showing changes such as PTEN mutations and microsatellite instability, and type II tumors demonstrating P53 and Her2/neu overexpression.[4-7]

Initial Management

Because the majority of patients present with bleeding, the diagnosis of endometrial cancer is usually made based on endometrial biopsy or curretage. Following diagnosis, total hysterectomy and bilateral salpingo-oophorectomy remains the standard of care, and the most definitive method of evaluating the extent of disease. Whether or not lymphadenectomy is required remains controversial. Given the additional logistic complexities of pelvic and para-aortic node dissection, the added operative time and perioperative risk (in a population that is often obese with several co-morbidities) should be considered. In addition, extensive lymphadenectomy usually carries a 23% risk of lymphodoema.[8]

Options for Fertility Preservation

For women of reproductive potential, fertility preservation, i.e. medical therapy without hysterectomy, may be a reasonable option and has become an increasingly relevant issue facing gynaecologic oncologists. However, careful patient selection is required and hysterectomy is recommended once childbearing has been completed due to significant rates of recurrent disease.[9] Ideal candidates for fertility preservation are women who desire future fertility and have apparent low risk features (grade 1 and no myometrial invasion) based on a non-invasive evaluation of extent of disease.

Prior to medical therapy, the evaluation includes pelvic MRI for assessment of tumour size and possible myometrial invasion; this appears to be the most sensitive test for this purpose.[10, 11] Endometrial curettage should also be performed to "debulk" intrauterine endometrial disease and provide as comprehensive an assessment of the tumour as possible. Patients with suspected myometrial invasion and/or those with lymphovascular space invasion (LVSI), face an increased risk of more extensive disease.

Therefore, fertility preservation should be individualised with careful consideration of the benefits and risks of treatment.

Approach to Adjuvant Treatment

The approach to adjuvant treatment is based on an assessment of risk for both disease progression and death from disease. Considerations for treatment takes into account risk factors and can be used to stratify women into low-risk, intermediate-risk, and high-risk categories:

Low-risk

Grade 1-2 tumours, minimal to no myometrial invasion, and absence of lymphovascular space invasion (LVSI).

Intermediate-risk

Cancer confined to the uterus but invades the myometrium (stage IA or IB) or demonstrates occult cervical stromal invasion (stage II).

Additional factors are also used to stratify women into high- and low-intermediate risk disease, including deep myometrial invasion, grade 2 or 3 differentiation, or the presence of lymphovascular invasion (LVSI).

High-intermediate risk criteria used by GOG include: Patients of any age with all three pathologic factors (Grade 2 or 3, Outer 1/3 invasion, LVSI), patients 50 to 69 years old with two factors, or patients who are 70 years or older with only one factor. Others lacking these factors are considered to be at low-risk.[12]

High-risk

Women with clear cell or serous carcinomas regardless of stage are considered to be in the high-risk group. This also includes women with stage III endometrial cancer that has been optimally resected.

Adjuvant Treatment Based on Risk

Low Risk and Low Intermediate-risk

Women with low intermediate-risk endometrial cancer have an excellent prognosis following surgery alone. As such, the risks of adjuvant radiation therapy likely outweigh any benefit of treatment.[13, 14]

High Intermediate-risk

Women with high intermediate-risk warrant adjuvant therapy. Uncertainty still exists, however, in the type of adjuvant therapy that should be prescribed, and to what clinical endpoint.

Because the majority of recurrences in GOG 99 and PORTEC occurred at the vaginal apex, vaginal brachytherapy was thought be equally as effective compared to external beam whole pelvic radiation therapy (WPRT), but with significantly less treatment related side effects and long term complications.[12, 15]

This was shown in the PORTEC 2 trial, which compared WPRT to vaginal brachytherapy in a high intermediate risk group of women. Treatment resulted in similar vaginal recurrences without significantly effecting either locoregional or distant recurrence rates.[16] This was also confirmed in the combined ASTEC/EN.5 study.[17] Overall, it appears that the addition of adjuvant radiation confers only a local control benefit to these women, and vaginal brachytherapy may be a more appropriate treatment strategy to address this local recurrence risk.

Lingering concerns persist amongst some treating physicians that in unstaged women this may not be sufficient. Current clinical research trials in the subgroup of "high intermediate" risk women are focusing on addressing these regional and systemic failures with different treatment approaches, specifically the addition of chemotherapy.

Is There a Role for Chemotherapy?

Adjuvant chemotherapy has been evaluated in two previous randomised prospective clinical trials in intermediate risk populations. In a Japanese GOG study, WPRT was compared to at least 3 cycles of cyclophosphamide, doxorubicin, and cisplatin (CAP regimen) in women with FIGO 1988 stage IC-IIIC tumors with >50% myometrial invasion; approximately 75% of the women enrolled had stage IC-IIB tumors.[18] Progression free and overall survival rates were similar between treatment groups (PFS 82% vs. 84% and OS 87% vs 85% for CAP vs. WPRT, respectively), as well as patterns of recurrence, however, a subgroup analysis of a differently defined "high intermediate" risk group of women showed improved progression free and overall survival with chemotherapy compared to radiation (PFS 84% vs. 66% and OS 90% vs. 74% for CAP vs. WPRT, respectively).

A similar Italian study evaluated women with stage IC grade 3, stage II with deep myometrial invasion, or stage III disease to either WPRT with or without extended field radiation or five cycles of CAP chemotherapy.[19] In this study, however, only one third of women had stage I-II tumours. Progression free and overall survival rates were again similar between treatment groups (3 year PFS 69% vs 68% and 3 year OS 78% vs. 76% for WPRT vs. chemotherapy respectively) but patterns of failure were slightly different, with chemotherapy appearing to decrease distant recurrences and radiation decreasing local failures.

The current phase III clinical trial of the GOG, GOG 249, randomises "high intermediate" risk women to either WPRT versus vaginal brachytherapy plus three cycles of carboplatin and paclitaxel chemotherapy. The primary endpoint of this study is recurrence free survival with overall survival as a secondary endpoint.[20] We strongly support the enrollment of women in these clinical trials.

High-Risk

For women with high risk disease, systemic chemotherapy has replaced the use of adjuvant radiation. This was based on the results of GOG 122, a randomised phase III trial that compared whole abdominal radiotherapy to 8 cycles of cisplatin and doxorubicin chemotherapy in

stage III/IV disease with minimal residual tumor burden following surgery. Chemotherapy significantly increased progression free (hazard ratio 0.71, 95% CI 0.55-0.91) and overall survival (HR 0.68, 95% CI 0.52-0.89). This translated to 5-year progression free survival rates of 42% versus 38%, and overall survival rates of 53% and 42% for chemotherapy versus radiation, respectively.[21]

Expanding on systemic based regimens, GOG 177 evaluated women with measurable stage III/IV and recurrent endometrial cancer with cisplatin and doxorubicin with or without the addition of paclitaxel (TAP regimen). Approximately 40% of the women enrolled were being treated in the adjuvant setting, and overall half had prior radiation. Both progression free and overall survival favoured the addition of the taxane, but with expected increased toxicity.[22]

More recently GOG 209 compared carboplatin and paclitaxel to the TAP regimen in a similar cohort of women, and preliminary results based on an interim analysis of this randomised phase III non-inferiority trial have recently been presented at the Society for Gynecologic Oncology's 43rd Annual Meeting.[23] As presented, the median overall survival differed by 3 months (37 versus 40 months for carboplatin and paclitaxel versus TAP, respectively, HR 1.05, with the upper boundary of the 90% confidence limit at 1.16). Having previously defined the upper limit for inferiority at 1.2, this study suggests that carboplatin and paclitaxel is not inferior to TAP. Researchers and clinicians eagerly await the final results and publication of this trial.

Is There a Role for Combination Chemoradiation?

While platinum and taxane based chemotherapy regimens are now considered the standard for advanced stage, high risk endometrial cancer, combined modality therapy remains an active area of clinical research. Previously, GOG 184 explored the addition of either cisplatin and doxorubicin or the TAP regimen to WPRT with or without extended field radiation in women with surgically resected stage III disease. Both arms had similar progression free survival rates (62% versus 64%) with expected added toxicity in the TAP arm.[24] In contrast, combined results from a Nordic Society of Gynaecological Oncology/European Organisation for the Research and Treatment of Cancer (NSOG/EORTC) and a Gynaecological Oncology group at the Mario Negri Institute (MaNGO) study which randomised high risk Stage I-III patients to WPRT versus WPRT plus chemotherapy (doxorubicin/epirubicin, cisplatin/carboplatin or paclitaxel) demonstrated a significant 37% reduction in recurrence risk in the chemotherapy group.[25]

GOG 258 is the current clinical trial available for women with optimally resected Stage III/IV endometrial cancer, and is evaluating cisplatin and concurrent tumor directed irradiation followed by carboplatin and paclitaxel versus carboplatin and paclitaxel alone. The primary endpoint of this study is recurrence free survival with a planned sample size of 804 women; overall survival is a secondary endpoint.[26] Again, we strongly support enrollment of women on this and other trials investigating novel treatment strategies for advanced stage, high risk endometrial cancer.

Conclusions

This summary has hopefully provided a contemporary, evidence based approach to treatment strategies for differing categories (low/intermediate, high-intermediate, and high risk) of endometrial adenocarcinoma. Further clinical research with respect to every step in the diagnosis, evaluation, and treatment of this disease is necessary. Currently, trials evaluating new radiologic modalities at the time of diagnosis are underway. There is also increasing interest in the concept of sentinel lymph node detection and evaluation in this disease site. Molecular profiling of tumors as an adjunct or alternative to traditional clinical and pathologic risk stratification systems is a very interesting concept being explored; this is currently utilised in other solid tumors, such as breast and colon cancer, and affects decisions regarding the use of adjuvant therapy. Finally, novel chemotherapeutics and particularly biologic agents that focus on common aberrant molecular pathways in endometrial cancer are reaching fruition in phase II clinical trials.

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Sexual Dysfuction in Women with Diabetes

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Introduction

Diabetes is a chronic disease responsible for multiple medical, sexual and psychological complaints. The main objective in the management of a patient with diabetes is to maintain a healthy status and quality of life and to avoid complications.[1-4] Nowadays, one of the diabetes related concerns receiving more attention is sexual dysfunction. This condition has been studied primarily in men. Multiple studies have shown that men with diabetes have an increased risk of erectile dysfunction and that it happens at younger ages than in general population. Moreover, sexual dysfunction is associated with the duration of the disease and with the poor metabolic control of diabetes.[1,5] However studies on sexual dysfunction in women with diabetes have not been developed until recent times.[5-8] The lack of clear sexual dysfunction definitions and standardised instruments to measure female sexual function as well as the presence of social taboos about sexuality may explain this circumstance. Because sexuality is a complex phenomenon that involves biological, psychological and social aspects, most of the studies up to date are questionable.[5,7]

Prevalence of Sexual Dysfunction

The prevalence of sexual dysfunction in women varies from 43% in U.S.[9] to 78.4% in Ecuador.[10] Nevertheless, it has been described that the prevalence of sexual dysfunction in women with diabetes arrives at 85%.[8] This figure varies depending on the type of diabetes, ranging from 17 to 71% in patients with type 1 and from 14 to 55% in type 2. However, these numbers might be over or underestimated.[4,7,11] The final analysis of the Diabetes Control and Complication Trial by Enzlin indicated that 35% of women with type 1 diabetes (T1D) suffer any type of sexual dysfunction; data that are very similar to that found in several studies carried out previously[11] but minor than the observed in Latin-American women with type 2 diabetes (T2D).[12,13]

A recent study described that 40% of women ceased their sexual activity between 40 and 60 years of age.[13] In the United States, only 50% of women between 60 and 74 years old have a sexual partner, a percentage far lower than the 86.4% recognised in younger women.[13] The reasons are not well understood, but several factors have been suggested, such as female sexual dysfunction, male impotence, absence of a partner or disorders like diabetes or other metabolic disease.[13]

Sexual dysfunction in women includes persistent or recurrent disorders of sexual interest, desire, arousal, orgasm and pain or difficulty to complete intercourse. In women with diabetes mellitus have been detected that the main problems are low desire and decreased lubrication reported in 17-85% and 14-76% of women respectively.[5] Disorders of orgasm and pain were less common and reported in 1-66% and 3-61% of women respectively.[11] Other concerns described in some studies include decreased sensitivity of the clitoris and increased vaginal discomfort.[3]

Several factors may impair these complaints such as menopause that are related to a decreased oestrogen production that leads to decreased vaginal lubrication and dyspareunia, or the ageing process that is related to other co-morbidities.[14,15]

Clearly, diabetes mellitus significantly increased the risk of female sexual dysfunction (FSD). A study in Peruvian

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postmenopausal women with diabetes found up to 75% of cases with sexual dysfunction. On the contrary, in diabetic Turkish women, Doruk and associates found a 42% rate of sexual dysfunction.[16] The lower prevalence of FSD among Turkish women can be explained by the fact that 69% of the women were premenopausal, who have a lower prevalence of sexual dysfunction.[17]

Other metabolic diseases that have been related to sexual dysfunction are hypothyroidism and obesity.[18] In a comparative study, diabetic, obese and hypothyroid women have reduced scores in the female sexual function index (FSFI) questionnaire when compared with healthy women (Figure 1).[4]

In a recent review, the main organic causes of sexual dysfunction among men and women with diabetes were erectile dysfunction and vaginal lubrication (Table 1).[1] However, analysis of the different studies that assess sexual function using FSFI revealed that, desire was the most affected being hypoactive sexual desire disorder the most frequent sexual dysfunction in women with DM.[19-21]

Many studies have been designed to evaluate sexuality in diabetic women; however, most of them used methodologies that are inadequate at the present time.[22] Excluding inconsistent data;[20] the majority of studies focused on sexuality in DM women point out a tendency towards impairment since higher rates of orgasmic dysfunction,[23] desire dysfunction problems in lubrication anorgasmia and dyspareunia have been described.[24,25]

Causes of Sexual Dysfunction in Diabetic Women

Among the reasons proposed for the higher prevalence of sexual dysfunction in women with diabetes are neurological, hormonal and vascular changes.[26] As these phenomena are impaired with increasing years with the disease, a worsening in the FSFI scores of these women would be expected; however, no differences were observed comparing women with 5, 10 or 15 years of DM evolution.[12] These data suggest that sexual dysfunctions begin early in the evolution of diabetes, probably associated with the first metabolic and/or vascular alterations that originate this disease. Another factor that deteriorates sexuality in DM women is poor metabolic control. Similarly to the observed association between diabetic men with erectile dysfunction and poor metabolic control,[27] diabetic women with inadequate metabolic control have significantly lower total FSFI scores.[12]

Sexual Desire	Sexual Arousal	Orgasm
Man Some influence of sexual desire possible	Problems with erection in 50% of diabetic men 5 times more than in the normal population	Retrograde ejaculation Partial ejaculation incompetence
Women Some influence of sexual desire possible	Problems with vaginal lubrication in 30% of diabetic women 2 times more than the normal population	No influence

Table 1. Comparison of the specific influence of diabetes on sexual dysfunctions in women and men.

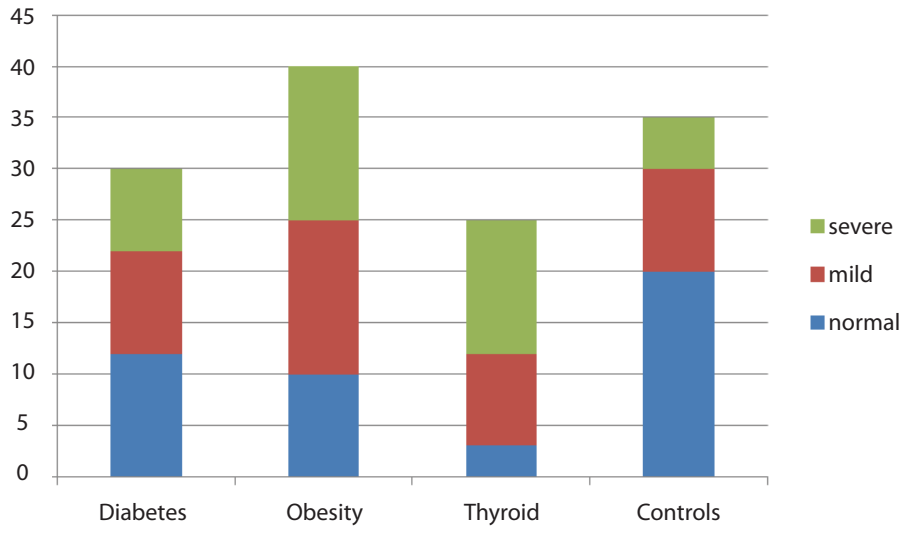

Figure 1. Frequency of normal, mildly impaired, and severly impaired sexual function in women, as assessed through the Female Sexual Function Index.[4]

Endothelial Dysfunction

Diabetic neuropathy leads to decreased sexual stimuli receptors and deregulation of the endothelium; therefore, leading to a reduction of blood supply to the vagina and causing loss of lubrication, atrophic changes and dyspareunia.[26]

Pre-menopausal women with diabetes may lose the protective mechanisms that have been associated with a lower incidence of macrovascular disease in women. Cholesterol, systolic hypertension and endothelial dysfunction also appear to be important factors influencing the incidence of vascular disease in diabetic men and women.[28]

The reduction of nitric oxide that occurs in diabetic patients is related to an increase of vascular complications as well as reducing vascular congestion during vaginal intercourse,[26] this would cause a decrease in arousal, as physiological arousal phase is accompanied by a pelvic and external genitalia vasocongestion.[11,26] The congestion of the clitoris is a haemodynamic phenomenon in nature, characterised by smooth muscle relaxation and it is thought that this could have an impact causing anxiety by the lack or the inability to maintain sufficient sexual excitement. One study administering doses of 100mg of sildenafil assessed the effect of this drug on clitoral blood flow in premenopausal women suffering from diabetes type 1 finding a decreased resistance and increased clitoral arterial blood flow.[29] This effect was reflected in an increased excitement in these women and although there is a need for further studies these data suggest that PDE5 inhibitors may be useful in the treatment of sexual dysfunction problems in patients with diabetes.[29]

Loss of Vaginal Lubrication

Tyrer *et al.* studied the effects of diabetes on vaginal lubrication finding a decreased lubrication in 10% of diabetic women compared with 2% of controls, however failed to establish a correlation between lack of lubrication and vascular disease.[1,2,3] In addition, women with diabetes have an increase in the prevalence of vaginal infections; this together with a decrease of lubrication can contribute to pain during sex.[2] Vaginitis, which may be infectious and non-infectious affects sexual function adversely as well as causes dyspareunia. Unfortunately often their presence is not recognised because it can occur without symptoms.[11] The results of some studies showed a higher prevalence of pain in women with DM compared with controls without, while others show no correlation.[1]

Endocrine Disorders

Diabetes adversely influences systemic endocrine function in both men and women.[26] In animal studies, diabetes alters the structure of the genital tissue attenuating the expression of progesterone and androgen receptors which resulted in changes in vaginal and clitoral congestion.[29] Additionally diabetes mellitus altered the expression of the oestrogen receptor leading to a decrease in the binding of oestrogen and/or attenuating receptor signalling, resulting in a decreased expression or activity of oestrogen-dependent proteins in the vagina.[26]

In addition, in postmenopausal women hormone replacement therapy (HRT) may improve sexual desire, vaginal lubrication, sexual pleasure and genital sensation.[14] However, HRT in diabetic women are reported to be used less frequently than in the general population.[4]

Psychological Factors

Recent data suggest a major role of psychological and social factors in sexual dysfunction.[3,5,6,11] Prospective studies and meta-analysis revealed a significant correlation between the presence of depressive symptoms and the prevalence of sexual dysfunction in women with DM. However, it is unclear whether these factors are cause or result of sexual dysfunction.[3,28] Newman and Bertelson assessing the incidence of psycho-sexual problems in 81 diabetic women treated with insulin suggested that sexual dysfunction in diabetic patients is mainly by psychogenic origin. Loss of attractiveness has been reported in 34% of type 1 diabetic women, compared with 19% in T2D. Influencing factors were: weight gain and disfigurement of the place of injection.[2] The feelings of loneliness and isolation were also more common in women with T1D (40%) than in T2D (21%). Moreover, in diabetic women sexual dysfunction was associated with lower marital satisfaction, depressive symptoms, poor adaptation to diabetes, the greater impact of diabetes on daily life and low satisfaction with treatment.[2,7]

Other associated factors can be considered, Meeking *et al.* reported that 12% of interviewed women believe that concerns and fears associated with the influence of diabetes in pregnancy affect the sexual intercourse.[11] Moreover, Tyrer *et al.* reported that incidence of sexual dysfunction is more common among the partners of women with diabetes than partners of non-diabetic control women.[7] However, only 9% of the sample of patients felt that diabetes and its associated complications damage their relationship. The long-term effects of diabetes on the relationship were not studied.[7]

Neuropathy

Early research on diabetes and female sexual function was limited mainly to evaluate the influence of neuropathy in orgasm. However, recent studies have demonstrated clearly a relationship between neuropathy and reduced orgasmic sensation.[2] The orgasm has been reported as one of the least understood aspects in the female sexual response and may be that brain influence in the orgasmic pleasure compensates the reduced genital sensation. This scenario creates difficulties in trying to establish the effects of diabetic neuropathy in the female orgasm. The lack of genital sensation is also associated with ageing so it is difficult to differentiate between the effects of neuropathy and the ageing process. Neuropathy can inhibit the activation of nitric oxide and affects the vascular response during sexual stimulation.[26] In a study by Leedor, neuropathic women reported more symptoms of sexual dysfunction compared to patients without neuropathy and controls.[26] In addition, clitoral nerve lesions were similar to those observed in men with impotence, but these data has not been corroborated.[26]

Others

Female sexual function is greatly influenced by the quality of the partner's sexuality.[30] Additionally, many other factors have been proposed such as age, duration of diabetes, body mass index, glycemic control, HbA_{1C} concentration, menopausal status, hormonal contraceptive use and complications of diabetes, however, most data are contradictory.[2]

Therapeutic Options

A large number of well designed randomised clinical trials assessing the effects of medical interventions on female sexuality have been published recently. On the other hand, comparisons between studies are difficult since in most cases no validated psychometric instruments have been used. Previously to apply results of studies on female sexual dysfunction to daily clinical practice, existing limitations should be clarified.[14] Moreover, in women with diabetes the studies are scant. Some therapeutical alternatives are discussed now.

Diet

In a study made by Guilianol *et al.*, a positive association between adherence to Mediterranean diet and FSFI score, was found. Diabetic women with the highest adherence to the Mediterranean diet had the lowest prevalence of sexual dysfunction. This association was independent of various anthropometric, lifestyle and clinical characteristics.[8] The Mediterranean diet is rich in plan food, such as fruit, nuts, legumes, cereals, and fish, with olive oil as the primary source of mono-unsaturated fat and low to moderate intake of wine. This diet has been associated with a number of healthful outcomes, including reduced risk of cardiovascular disease, cancer and mortality.[8] Several mechanisms have been proposed to mediate this protection, and their overall description includes the anti-inflammatory, antithrombotic and anti-oxidative effects of Mediterranean diet.[8]

Androgens

Recent data suggest that androgens could be a useful option for sexual dysfunction in menopausal women. In addition, androgens could also improve quality of life.[31] A meta-analysis by Zweifel showed that androgens alone or combined with oestrogens improve the mood more than oestrogens alone.[29,32]

A study by Castelo-Branco *et al.* showed that adding methyl-testosterone to hormone therapy in post menopausal women with sexual dysfunction, improved quality of life and sexuality.[31] Davis *et al.* pointed out that testosterone and oestrogen combined therapy administered to postmenopausal women improved sexual activity, satisfaction and pleasure and orgasm frequency more than oestrogens alone.[31] However, there are no evidence from studies in patient with diabetes.

Sildenafil

Preliminary findings on the use of sildenafil demonstrated positive effects in sexual arousal and orgasm in selected women and premenopausal woman with T1D.[14] However, placebo-controlled studies in females with sexual arousal disorder yielded inconclusive results.[14] Actually, sildenafil use has not been approved for female sexual arousal disorder.[14]

Psychological Therapies

Psychosocial interventions are excellent for addressing most categories of sexual dysfunction in patients with diabetes. However, one of the barriers to this type of approach is patient reluctance. Sexual symptoms may be conditioned and maintained as an unconscious coping strategy for other underlying problems. Psychosocial interventions include basic counselling, physiotherapy and psychosexual intervention.[32]

Conclusion

Sexuality disorders are particularly frequent in women with diabetes. This condition has a negative impact on the quality of life and often needs medical support including counselling and pharmacological therapies. Further studies are needed to elucidate in full the mechanisms underlying the evident differences between male and female sexual function.

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Sex Steroid Hormones and Diabetes

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Introduction

In addition to reproductive actions, sex steroid hormones have other biological roles. Variations in the levels of these hormones, either normal or pathological, may have significant influence in the onset of several diseases, metabolic syndrome components included, as well as in the behaviour of tissues and organs. For instance, diabetes mellitus (DM) is associated with gender-specific changes in sex hormones: men develop cardiovascular diseases at an earlier age than pre-menopausal women, who seem to be protected by the antioxidant properties of oestrogens.[1,2]

Not only gender differences exist, but also several factors such as age, race, lifestyle and diet may contribute to modify the prevalence of metabolic syndrome.[1]

However, the mechanisms responsible for these associations are not well understood. Imbalances in sex steroid hormone levels may be associated with metabolic profile, and this may negatively impact upon sexual function, hormone replacement therapy may improve both disorders.

The aim of this chapter is to analyse the relationship between sex hormones and diabetes, as well as the possible effects of hormone therapy.

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Diabetes and Testosterone

Hypogonadism and Type 2 Diabetes

Studies over the last few years have clearly established that at least 25% of men with type 2 diabetes (T2D) have abnormally low free testosterone concentrations in association with inappropriately low LH and FSH concentrations. Another 4% have low testosterone concentrations with elevated LH and FSH concentrations.[3] Additionally, there is evidence that low testosterone levels may predict the development of T2D.[4] The Endocrine Society, therefore, now recommends the measurement of testosterone in patients with T2D on a routine basis.

Hypogonadism is generally suspected when morning levels for total testosterone are <300 ng/dl and clinical signs and symptoms typically associated with androgen deficiency are present, such as erectile dysfunction (ED), low libido or mood disturbances. Although testosterone levels and erectile function are known to decline as men age, men with type T2DM have a particularly high prevalence of hypogonadism and ED.

This population also has an increased risk for cardiovascular diseases, as well as exposure to other metabolic and cardiovascular risk factors, such as obesity.[5] Interestingly, ED and male hypogonadims are recently recognised as possible predictors also for other metabolic diseases and cardiovascular events.[6,7,8] The specific mechanisms through which hypogonadims may affect cardiovascular health have not yet been clarified, but clinical and animal evidences show that testosterone plays a favourable effect upon vascular reactivity, inflammation, cytokine production, adhesion molecule expression, serum lipid concentration and haemostatic factors.[9]

Physiopathology

Considering hypogonadism and diabetes, the association could be due to the reduction in sex hormone-binding globulin (SHBG) induced by insulin resistance, which is observed in diabetic patients.[10] Not only total testosterone is decreased, but also a reduction in free testosterone exists.[9] Androgens regulate fat

mass and distribution, and variations in the body composition determined by androgens could affect insulin sensitivity.[7] In fact, obesity may be the most important contributor to the presence of hypogonadism in T2DM. Besides, studies in animal models of both type 1 diabetes (T1D) and metabolic syndrome[11] suggest that hyperglycaemia and insulin resistance play a major role in inducing hypogonadism. Thereby, loss of androgen function leads to diabetes, and loss of glycaemic controls leads to hypogonadism. But the question to be raised is whcih of both comes first? A complex bi-directional interrelationship between both conditions exists.[7] The relationship of T2DM and obesity with low testosterone is also bi-directional: low testosterone predispose to obesity while obesity perpetuates hypogonadism.[12]

The second question could be whether hypogonadism also occurs in T1DM. Comparing the prevalence of hypogonadism in age-matched T1DM and T2DM men, 6% of T1DM men were hypogonadal as compared to 26% of T2DM men.[13] In addition, SHBG in T1DM was higher than in T2DM men. Thereby, hypogonadism does not occur commonly in T1DM and is not a function of diabetes or hyperglycaemia *per se*. However, total testosterone and free testosterone are also inversely related to body mass index (BMI) even in T1DM.[12]

Testosterone Therapy

After recognising T2DM as a risk factor for hypogonadism, the specific metabolic effect of testosterone replacement therapy (TRT) in hypogonadal diabetic subjects is a topic of discussion.

Short-term studies of TRT in hypogonadal men with T2D have demonstrated an increase in insulin sensitivity, improving glycometabolic control (glycaemia and HbA1c). In addition, a decrease in waist circumference and a reduction in triglyceride levels are suggested. However, the data on the effect of testosterone replacement on other cardiovascular risk factors, such as cholesterol, blood pressure and C-reactive protein concentrations are inconsistent.

As far as sexual function is concerned, testosterone treatment increases libido, and improves sexual thoughts, satisfaction, motivation and intercourse frequency.[7] Although TRT does not completely improve erectile dysfunction and thus, phosphodiesterase (PDE5) inhibitors may be required, TRT could restore responsiveness to this drug.[7] Nevertheless, further studies are required to confirm these preliminary results.

It is important to note that current recommendations do not suggest widespread TRT in subjects with T2DM in the absence of laboratory and other clinical evidence of hypogonadism.[14]

In conclusion, several professional societies have recommended screening men with T2DM for testosterone deficiency, and this alteration may have clinical relevance in the development and control of diabetes. While hypogonadism and ED have emerged as predictors of cardiovascular disease and may respond to the lifestyle changes commonly recommended for patients with diabetes and the metabolic syndrome, the literature on whether treatment with testosterone supplementation affects outcomes beyond well-being and sexual function is still emerging.[5,12] Trials of longer duration are clearly required to definitively establish the benefits and risks of testosterone replacement in patients with T2DM and low testosterone.[3]

Diabetes and Oestrogens

Oestrogen Protection Against Diabetes

After menopause, women are at an increased risk to develop visceral obesity due to the loss of endogenous ovarian hormone production. Effects of oestrogens are classically mediated by the two nuclear oestrogen receptors (ERs) α and β. In addition, more recent research has shown that the intracellular transmembrane G-protein-coupled oestrogen receptor (GPER) originally designated as GPR30 also mediates some of the actions attributed to oestrogens.[15,16] Oestrogen and its receptors are important regulators of body weight and insulin sensitivity, not only in women but also in men.[17]

Elevated estradiol and leptin concentrations observed in obese men can probably explain partially the hypogonadotrophic effect of obesity. Testosterone and androstenedione in men can be converted to oestrogen by aromatisation in extraglandular tissues, and the rate of aromatisation increases with age and obesity. Nevertheless, it is not yet known if hypogonadal T2DM males have higher or lower oestrogen levels than eugonadal T2DM males.[12]

Coming back to females, oestrogens maintains energy homeostasis via ERα and ERβ, by suppressing energy intake and lipogenesis, enhancing energy expenditure, and ameliorating insulin secretion and sensitivity.[18] Also in multiple animal models of diabetes, it has been demonstrated in females that relative protection from β-cell failure exists, and the hormone 17β-estradiol (E2) partly mediates this benefit.[19] Another example is the lower prevalence of diabetes in premenopausal women, especially diabetic syndromes with insulin deficiency, suggesting again the female hormone protection.[20] E2 favours islet survival, lipid homeostasis and insulin biosynthesis. It also improves insulin sensitivity and energy homeostasis.

Oestrogen Replacement Therapy

Oestrogen replacement therapy reduces the incidence of diabetes in postmenopausal women,[21] although it is not an acceptable treatment. However, selective oestrogen receptor modulators, such as tamoxifen, may be more appropriate. Raloxifene does not seem to influence β-cell function in healthy postmenopausal women, and the new-generation SERMs are currently being evaluated. Nevertheless, further investigation represents a novel therapeutic way in diabetes.[20]

Apoptosis is the major mode of pancreatic β-cell death in both T1DM and T2DM. An association between oestrogens and T1DM also exists.

Thereby, hypogonadotropic hypogonadism, hypoestrogenism, menstrual irregularities, polycystic ovaries and early menopause have been described in T1DM women. In spite of the beneficial effects of oestrogen with regard to insulin action and secretion in healthy women, it is striking that women with T1DM seem to lose these beneficial metabolic effects of oestrogen. Some of the problems observed in T1DM women may be in part due to the relationship between decreased oestrogen levels and insulin action.[22]

Several studies try to define the role of testosterone on diabetes and the relationship with sexual problems in men, but there is a lack in extensive research related to diabetic women and sexual dysfunction.[2] Empirical studies do not show uniform results, but it appears that diabetic women experience more frequent sexual dysfunction than age-matched healthy controls. The most frequently cited dysfunctions are desire and arousal disorders, such as lubrication difficulties, while orgasmic capacity appears to be less affected. The role of diabetic complications is controversial, and individual coping with the disease and the quality of the relationship are also contributing factors.[23]

Diabetes and Congenital Hypogonadims with Chromosomal Aberrations

After describing the role of sex steroid hormones in the onset and development of the metabolic syndrome, it would be interesting to analyse these dysfunctions in patients with congenital hypogonadism due to chromosomal abnormalities, such as Turner syndrome, Klinefelter syndrome or Prader-Willi syndrome.

Turner's Syndrome and Diabetes

Turner syndrome (TS) is the most common chromosomal abnormality in females, and affects 1 in 2,500 live female births. TS is the result of the absence or the abnormality of the second sexual chromosome, in at least one cellular line, and it is associated with a wide array of potencial abnormalities, most of them thought to be caused by haploinsufficiency of genes that are normally expressed in both X chromosomes. The cardinal features of TS are short stature and ovarian failure with insufficient sex steroids, which cause delayed puberty and primary amenorrhea in most cases. Oestrogen deficiency also causes bone loss, endothelial dysfunction, decreased insulin production, an abnormal lipid pattern, increased central adiposity and early atherosclerosis.[24,25]

In addition, TS has associated more prevalence of other subrogate cardiovascular risk factors as dyslipidaemia and diabetes mellitus due to insulin resistance.[26] T2DM is 2-4 times more common in TS subjects as compared to normal females, and tends to develop at a younger age, but it is usually mild and responsive to weight loss or monotherapy.[27] The primary pathogenic event is β-cell dysfunction, but insulin resistance also plays a central role and does not seem to be dependent of BMI, like in polycystic ovarian syndrome. However, obesity and elevated waist-to-hip ratio found in TS worse this defect. Hypertriglyceridaemia may be a consequence of hyperinsulinaemia and obesity.[24]

Klinefelter Syndrome and Diabetes

Klinefelter syndrome (KS) affects 1:660 men, being the most common sex-chromosome disorder in males. KS causes of infertility, hypergonadotrophic hypogonadism and learning disability, and affected subjects are described as tall, slim, broad hipped, narrow shouldered and small testes. Recently, an increased risk of metabolic syndrome, T2DM and unfavourable change in body composition has been described in KS patients.[28]

Epidemiological studies[29] showed a generally increased mortality risk, specifically from diabetes. Gravholt described a high incidence of the metabolic syndrome and insulin resistance in 70 patients with KS compared to an age-matched control group. Significantly more KS subjects had elevated fasting plasma insulin levels, a decrease in insulin sensitivity, increased LDL-cholesterol and a reduction in HDL-cholesterol (Gravholt 2010). Thereby, both epidemiological and clinical studies show clear evidence of increased risk of diabetes and metabolic syndrome in KS.

Treatment with testosterone is suggested to reverse the unfavourable body composition and to improve insulin resistance, although this is not supported by prospective randomised studies in patients with KS.[28]

Patients with a rare sex chromosome aneuploidy (48XXYY karyotype), as variant of KS, are also associated with DM. In a published case-report, biological exams of an adult with this syndrome showed hyperglycaemia, increased glycated haemoglobin, decreased high density lipoproteins, and decreased testosterone levels with increased basal and stimulated gonadotrophin levels.[30]

These congenital hypogonadims are perfect models to study the impact of sex steroids on different molecules related to diabetes. For instance, the adiponectin is an adipokine with antidiabetic properties. It forms multimers and the high-molecular weight (HMW) form most closely correlates with insulin sensitivity testosterone has been shown to alter the subform distribution of adiponectin, whereas the effects of oestradiol are equivocal. Host *et al.* investigated the influence of sex hormone replacement therapy (HRT) on circulating adiponectin, fasting lipids and insulin sensitivity in TS and KS patients.[31] He concluded that short time HRT (oestrogens and progestagens) suppressed HMW and total adiponectin levels in TS patients. Nevertheless, testosterone treatment in KS patients did not have effect on these parameters. In both groups, either adiponectin or HMW subform seemed to play a greater role in mediating insulin sensitivity. Thereby, in TS and KS patients, exogenous sex hormones have different effects on adiponectin than previously reported healthy patients, or patients with other hormonal defects, such as polycystic ovary syndrome.[32]

Prader-Willi Syndrome and Diabetes

Finally, Prader-Willi syndrome (PWS) is a complex genetic disorder caused by lack of paternally expressed genes in region q11-13 on chromosome 15. PWS is characterised by short stature, muscular hypotonia, mild-to-moderate intellectual disability, hypogonadism, hyperfagia and risk of severe obesity from early childhood. The cause of the abnormal body composition is not completely known, but it has been ascribed to the impairment in the activity of the growth-hormone-IGF system and to the partial hypogonadism. The relatively reduced amount of visceral fat protects the PWS subjects from severe complications to the obesity; however, T2DM, dyslipidaemia and cardiovascular diseases have been frequently reported in PWS adults, with an estimated yearly mortality as high as 3%.[33] Here, another example of the relationship between hypogonadism and diabetes.

Conclusions

Although numerous factors are likely to contribute to the development of diabetes and its complications, the role of sex steroid hormones must be acknowledged.

Identifying underlying causes for hormonal imbalance in diabetic patients, as well as determination of genetic and age-dependent factors, will become important in identifying subpopulations in which hormonal replacement regimens will be more effective. Investigation into treating diabetic patients with adjunct hormonal therapies or steroid hormone receptor modulators holds much promise.[2]

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Angiogenesis: A Target for the Treatment of Ovarian Cancer

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Ovarian Cancer

Approximately 66,700 new cases of epithelial ovarian cancer were diagnosed in Europe in 2008.[1] In early stage disease, complete surgical excision is often possible and the prognosis is favourable, but approximately two thirds of patients present with advanced disease (FIGO stage III or IV). Only 32% and 18% of patients with FIGO stage IIIC and stage IV disease survive for five years, respectively.[2] Despite investigations into various methods, no screening test has proven effective in improving early detection rates and thereby survival.[3]

Surgical cytoreduction and platinum-based cytotoxic chemotherapy form the basis of primary therapy for advanced ovarian cancer. Many patients achieve complete clinical remission following primary therapy but, unfortunately, disease recurrence is common with many patients undergoing multiple lines of cytotoxic therapy, until acquired drug resistance limits therapeutic options. As the majority of patients with ovarian cancer present with advanced disease, it is vital that new therapeutic strategies are explored to overcome this resistance to chemotherapy and to prolong progression free (PFS) and overall survival (OS). One such strategy aims to target the angiogenic pathways, which play a key role in the physiology of the ovary and pathophysiology of ovarian cancer.

Tumour Angiogenesis

The term angiogenesis refers to the process by which new blood vessels are formed from pre-existing capillaries. Angiogenesis is a tightly regulated, multi-step process that is largely restricted to three physiological processes in the healthy adult; menstruation, embryonic growth and wound healing. Folkman originally proposed that solid tumours secrete angiogenic factors, which lead to angiogenesis within the tumour.[4] Without this development in vasculature, the tumour may not have the necessary oxygen and nutritional input to increase in volume greater than 1-2mm^3 and thus sustained angiogenesis is considered a hallmark of cancer.[5]

Hanahan and Folkman proposed that pro- and anti-angiogenic factors are tightly regulated in healthy tissues and that it is perturbation of this balance which leads to the acquisition of the angiogenic phenotype in tumours, the so called 'angiogenic switch'.[6] This switch in phenotype leads to sustained angiogenesis with highly disorganised tumour vasculature, resulting in poor blood flow and high vascular permeability. It is hypothesised that this disruption may impede the delivery of cytotoxic agents to the tumour and that normalisation of the tumour vessels with anti-angiogenic agents may, therefore, improve cytotoxic drug delivery.[7] This hypothesis, together with the observed difference between sustained tumour angiogenesis and the low activity of this process in healthy adult tissues, makes inhibition of angiogenesis an attractive therapeutic strategy.

The Vascular Endothelial Growth Factor (VEGF) family, which contains the prototypic target of anti-angiogenic therapy, is made up of at least seven members: VEGF-A to E and placental growth factors, PlGF-1 and 2. This family of growth factors and their receptors play a key role in physiological and pathological angiogenesis, making it an attractive target for targeted therapies. VEGF-A, commonly referred to as 'VEGF', is a vital mediator of tumour angiogenesis, which is secreted from most tumour cells and exists in four isoforms; VEGF-A165 being most commonly expressed in tumours.[8] Other isoforms differ in their affinity for heparin and may play distinct roles in angiogenesis.[9] VEGF was originally discovered through its role in the regulation of vascular permeability and it is now known that binding of VEGF-A to the tyrosine kinase receptors VEGFR-1(Flt-1) and VEGFR-2(KDR/Flk-1) promotes angiogenesis by activation of endothelial cells, promotion of cell survival signals, increased invasion and migration as well as increased vascular permeability.[10]

Angiogenesis in Ovarian Cancer

Angiogenesis has a key role in the physiological process of the female reproductive cycle and is necessary for follicular development. Intrafollicular levels of VEGF proteins increase during the initial phase of the ovulatory cycle and peak immediately prior to the luteal phase. Increasing concentrations of the angiogenic inhibitor angiopoietin-2 are associated with vessel regression and follicular degeneration towards the end of the luteal phase.[11]

Aside from the physiological response of the ovary to angiogenic

regulation, it is now clear that up-regulation of angiogenesis is crucially important in the pathophysiology of ovarian cancer. High levels of VEGF are released by ovarian cancer cells and VEGF over-expression appears to be associated with a poor prognosis in patients with primary ovarian cancer.[12] Conversely, decreased VEGF expression correlates with reduced angiogenesis, lower ascitic fluid volume and improved survival in mice.[13] These findings have led to a keen interest in exploiting angiogenic pathways in the treatment of ovarian cancer with the aim of inhibition of angiogenesis and, in turn, regression of ascites and tumour bulk.

Anti-VEGF Therapies

Bevacizumab

Bevacizumab, an anti-VEGF monoclonal antibody, was the first VEGF-targeting agent to be incorporated into large Phase III trials in ovarian cancer, following two Phase II studies showing significant single agent efficacy in patients with recurrent disease. The first of these Phase II studies involved the administration of bevacizumab 15mg/kg/q3w intravenously until disease progression in 62 patients with measurable, relapsed epithelial ovarian cancer. It reported a 21% radiological response rate and a median PFS of 4.7 months.[14] The second study, also published in 2007, enrolled 44 patients with heavily pre-treated, platinum resistant disease. This group used the same schedule and dose level of bevacizumab and reported a radiological response rate of 15.9% and median PFS of 4.4 months. The study closed early due to excessive toxicity, with a gastrointestinal perforation rate of 11.4% and an arterial thromboembolic event rate of 6.8%.[15] These data were particularly interesting as single agent responses were seen in many platinum resistant tumours, in which treatment options were limited.

Further Phase II trials have assessed the role of bevacizumab in combination with chemotherapy in the first line setting (Table 1) as well as in recurrent ovarian cancer (Table 2). In view of promising results in the Phase II setting, two large randomised Phase III trials have been conducted, in which bevacizumab was administered in combination with first line chemotherapy (Figure 1). The GOG-0218 study recruited 1873 patients with previously untreated epithelial ovarian cancer, who had stage III disease with macroscopic residual tumour or stage IV disease.[16] Patients were randomised into three arms: standard carboplatin and paclitaxel chemotherapy alone (arm I), chemotherapy with concurrent bevacizumab 15mg/kg (arm II) or chemotherapy with both concurrent and maintenance bevacizumab for up to 15 months (arm III). The primary end-point of PFS has been reached and has shown a statistically significant improvement in PFS in arm III compared to arm II (median PFS arm I 10.3 months; arm III 14.1 months, p <0.0001). Outcome comparisons with arm II showed no significant differences in PFS, suggesting that any benefits seen with the addition of bevacizumab might be attributable to the addition of maintenance bevacizumab therapy to the regimen. Examination of the

First Line Treatment					
Study	**No. of Patients (n)**	**Treatment**	**Response Rate (%)**	**Median PFS (months)**	**Median OS (months)**
Micha[36] 2007	20 Stage III or IV disease	Bevacizumab 15mg/kg plus carboplatin AUC5 and paclitaxel 175mg/m^2 q3w for six cycles	80	NR	NR
Penson[37] 2010	62 ≥IC Epithelial Mullerian Tumours	Bevacizumab 15 mg/kg/q3w for one year plus carboplatin AUC5 and paclitaxel 175 mg/m^2 6-8 cycles Median bevacizumab cycles 17	75	29.8	NR

Table 1. An overview of phase II trials assessing bevacizumab in the first line treatment of epithelial ovarian cancer.

Recurrent Disease						
Study	**No. of Patients (n)**	**Platinum Sensitivity**	**No. of Prior Regimens**	**Treatment**	**Median PFS (months)**	**Median OS (months)**
Monk[38] 2006	32	Platinum Resistant	≥2 Median 5	Bevacizumab 15mg/kg/q3w Median 6 Cycles	5.5	6.9
Burger[16] 2007	62	41.9% Platinum Resistant	≤2	Bevacizumab 15mg/kg/q3w Median 7 Cycles	4.7	16.9
Cannistra[15] 2007	44	Platinum Resistant	2-3	Bevacizumab 15mg/kg/q3w Median 5 Cycles	4.4	10.7 at study closure
Garcia[39] 2008	70	40% Platinum Resistant	≤3	Bevacizumab 10mg/kg/q2w plus cyclophosphamide 50mg/d Median 5 Cycles	7.2 (time to progression)	16.9
Smerdel[40] 2010	38	'Multi-resistant'	Median 5	Bevacizumab 10mg/kg/q3w Median 4 Cycles	5.9	8.6
Tillmanns[41] 2010	48	Platinum Resistant	≥1	Bevacizumab 10mg/kg/q2w plus nabpaclitaxel 100mg/m^2 d1, 8, 15/q4w	8.3	16.5
Kudoh[42] 2011	30	96% Platinum Resistant	≥1	Bevacizumab 2mg/kg weekly plus pegylated liposomal dozorubicin 10mg/m^2 d1, 8, 15/q4w	6.0	NR
McGonigle[43] 2011	40	Platinum Resistant	≤2	Bevacizumab 10mg/kg d1 and 15 plus topotecan 4mg/m^2 d1, 8, 15/q4w Median 8 Cycles	7.8	16.6

Table 2. An overview of phase II trials assessing bevacizumab in the treatment of recurrent epithelial ovarian cancer.

regulatory-level results, where CA125-based definitions of progression were excluded, demonstrated a six month improvement in PFS when arm III and arm I were compared (arm III median PFS 18.0 months v arm I 12.0 months, HR 0.645, p<0.0001). Early results do not show a significant difference in OS between the groups and indeed this was not the primary endpoint of the trial, perhaps in recognition of the widespread availability of bevacizumab for subsequent treatment. Notably, the rates of gastrointestinal toxicities of grade 2 or higher were reported at around 2.8%; much lower than in the Phase II studies. This may reflect the first line nature of this study in contrast to the heavily pre-treated Phase II cohorts of patients.

The ICON7 trial[17] also explored the use of bevacizumab in combination with first line chemotherapy but at the lower dose of 7.5mg/kg. It was an open label study with only two treatment arms: arm I had standard chemotherapy and arm II received bevacizumab during chemotherapy and as maintenance, totalling 18 cycles of bevacizumab over a 12-month interval. The trial included patients with early disease and, unlike GOG-0218, did not consider isolated CA125 rises as a marker for progression. The ICON group also reported a modest but significant improvement in median PFS (arm I 17.4 months vs. arm II 19.8 months p = 0.039) but notably the PFS curves unite at around 25 months. The OS data for the study as a whole are not yet mature. However, interim analysis has shown a statistically significant difference in median overall survival within a high-risk subgroup, largely containing patients with high stage, bulk residual disease. This subgroup analysis demonstrated a median OS of 28.8 months with chemotherapy alone and 36.6 months for those who also received bevacizumab (HR 0.64, 95% CI 0.48–0.85). Interestingly the similarity of PFS improvement in the experimental arms of both trials, where advanced stage high-risk patients are considered, raises questions about the optimum dose of bevacizumab in the first line setting.

The data from these studies have raised questions as to the optimum duration of bevacizumab therapy but also highlight the importance of identifying the subgroups most likely to derive benefit from treatment. To answer these important questions using a traditional model of another large randomised control trial is both time consuming and expensive. Validated biomarkers that are predictive for survival benefit could help guide clinical trial decisions and reduce the time spent treating those patients who are unlikely to benefit from this therapy.

It is unclear whether bevacizumab should be given beyond first progression. However, one trial has assessed the value of bevacizumab in recurrent ovarian cancer. The Phase III, OCEANS trial evaluated the efficacy of combination chemotherapy with bevacizumab in recurrent platinum sensitive ovarian cancer and reported initial findings in 2011. The patient population had first recurrence of ovarian cancer with ECOG performance status 0 or 1 and measurable disease (n= 484). They were randomised to receive carboplatin AUC4 plus gemcitabine 1000mg/m^2 in day one and day eight every three weeks for six cycles with either placebo or bevacizumab 15mg/kg every three weeks until progression. The initial results of the primary endpoint, PFS, were presented at the ASCO Annual Meeting 2011[18] and indicated a PFS advantage with the addition of bevacizumab to conventional chemotherapy. Median PFS in the chemotherapy arm was 8.6 months vs. 12.3 months with the addition of bevacizumab (HR 0.45, 95% CI 0.35-0.58, log rank p<0.0001). The similarity in PFS advantage between the first line trials and OCEANS raises the question of whether VEGF inhibitors should be administered at either first or second line treatment, or maybe both.

It appears increasingly clear that bevacizumab is active and has an

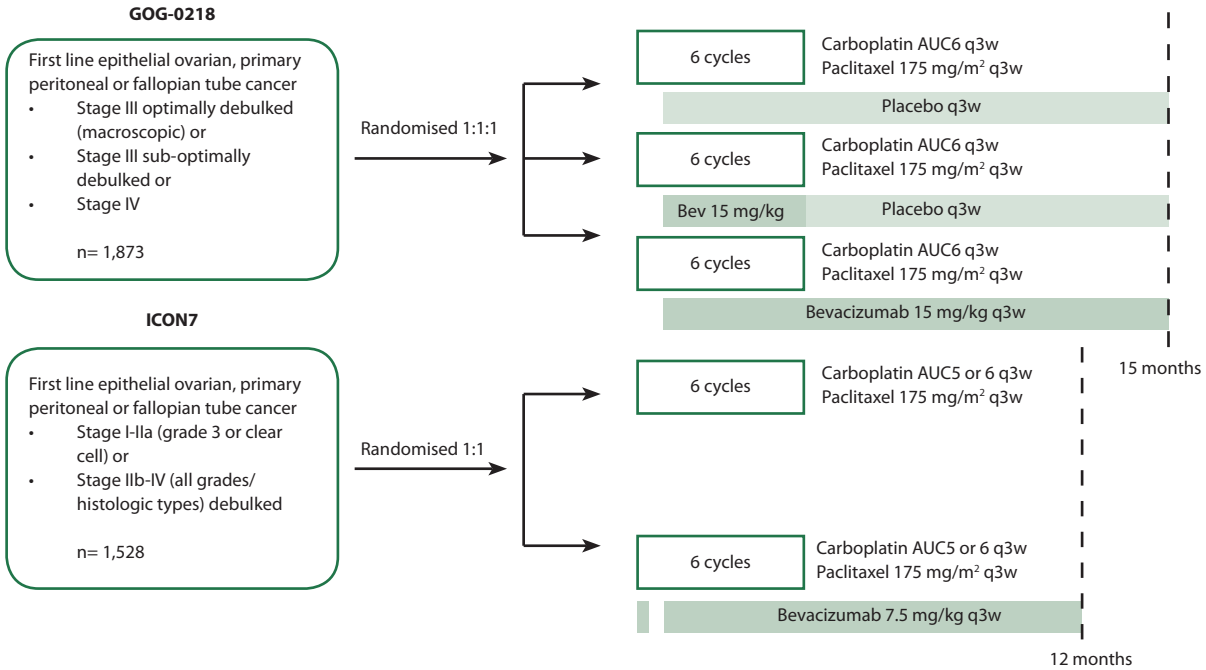

Figure 1. Study schema for the ICON7 and GOG-0218 phase III trials.

acceptable toxicity profile when used in combination with platinum based chemotherapy in the treatment advanced ovarian cancer. Several questions remain to be answered to ascertain the correct dose, duration and timing of treatment as well as to identify the correct patient population in which to use the drug.

Multi-targeted Inhibitors of Angiogenesis

Simultaneous targeting of multiple angiogenic pathways holds theoretical benefits over selective inhibition of the VEGF pathway alone but risks an increase in the potential associated toxicities. Several multi-targeted agents have undergone early phase testing in the treatment of ovarian cancer and are currently being further investigated in Phase III trials (Tables 3 and 4).

TKI	Targets	Current Trials
Cediranib AZD2171	VEGFR-1, -2 and -3, PDGFR, c-kit	Phase III ongoing- ICON6
Intedanib BIBF 1120	VEGFR, PDGFR, FGFR	Phase III ongoing- AGO-OVAR 12
Pazopanib GW 786034	VEGFR1-3, PDGFR, c-kit	Phase III ongoing- AGO-OVAR 16
Sunitinib SU11248	VEGFR, EGFR, PDGFR, c-kit	Phase II completed
Sorafenib	RAF-1, VEGFR-2, EGFR-3, PDGFR-β, FLT-3, c-kit	Phase II completed Neo-adjuvant Phase II terminated early due to excessive toxicity

Table 3. Selected VEGF tyrosine kinase inhibitors (TKIs) tested in epithelial ovarian cancer.

Cediranib

Cediranib is an oral tyrosine kinase inhibitor of VEGFR-1, -2 and -3 as well as c-kit. It has activity in recurrent epithelial ovarian cancer.[19] A Phase II trial of 47 patients with recurrent platinum resistant (65%) or sensitive (35%) disease investigated the efficacy of continuous daily cediranib. The daily dose was initially 45mg, dropping to 30mg after significant toxicities were observed in the first 11 patients. The primary end point was clinical benefit rate, defined as complete response, partial response or stable disease for greater than 16 weeks or CA125 non-progression for greater than 16 weeks. By this definition 30% of patients derived a clinical benefit. Twenty-three percent of patients were removed from the study due to toxicities. Notable grade 3 toxicities were hypertension (46%), fatigue (24%) and diarrhoea (13%). Grade 4 toxicities included CNS haemorrhage, altered lipid profile and elevated creatinine (n=1 for

Disease setting	Study	Stage	Chemotherapy	Targeted Agent	Duration	Primary End Point
JGOG weekly regimen	OCTAVIA[a] 1st line Phase II	I, IIa (g3) IIb-IV	Carboplatin AUC 6 q3w plus paclitaxel 80mg/m^2/wk	Bevacizumab 7.5mg/kg/q3w	12m	PFS
1st Line IP and wkly	GOG252[b] Phase III	III	Weekly iv paclitaxel plus iv carboplatin q3w or iv/ip paclitaxel plus iv carboplatin q3w or iv/ip paclitaxel plus ip cisplatin q3w	Bevacizumab 15mg/kg/q3w	6m	PFS
1st line TKi	AGO-OVAR12[c] Phase III	IIb-IV	Carboplatin AUC 5/6 plus paclitaxel 175 mg/m^2/q3w	Intedanib 200mg bd vs. placebo	28m	PFS
1st line TKi	AGO-OVAR16[d] Phase III	II+	Post-chemotherapy maintenance	Pazopanib 800mg/day vs. placebo	24m	PFS
Recurrent disease	ICON6[e] Phase III		Carboplatin plus paclitaxel or gemcitabine	Cediranib 20mg/day vs. placebo	12m	PFS/OS
Recurrent disease	GOG213[f] Phase III		Carboplatin plus paclitaxel or docetaxel	Bevacizumab 15mg/kg/q3w	Until Disease Progression	OS
Recurrent disease	Aurelia[g] Phase III		Physicians choice +/- bevacizumab	Bevacizumab 15mg/kg/q3w	Cross Over at Disease Progression	PFS
Recurrent disease	TRINOVA-1[h] Phase III		Paclitaxel 80mg/m^2 weekly	AMG 386 15mg/kg weekly vs. placebo	Until Disease Progression	PFS
Recurrent disease	TRINOVA-2[i] Phase III		Liposomal doxorubicin 50mg/m^2 q4w	AMG 386 15mg/kg weekly vs. placebo	Until Disease Progression	PFS

Table 4. Key trials currently investigating the role of targeted agents in the treatment of epithelial ovarian cancer.
Main rationale for trial:
a. To examine the role of bevacizumab in combination with weekly chemotherapy in the first line setting.
b. To compare the efficacy of bevacizumab plus intravenous chemotherapy with bevacizumab plus intraperitoneal chemotherapy in the first line setting.
c. To evaluate the efficacy of the TKI intedanib in combination with first line chemotherapy.
d. To determine whether pazopanib therapy is effective as maintenance therapy following first line chemotherapy.
e. To assess the efficacy and safety of cediranib as combination and maintenance therapy in patients with relapsed, platinum sensitive disease.
f. To determine if secondary surgical cytoreduction in addition to adjuvant chemotherapy with or without bevacizumab increases the duration of overall survival of patients with recurrent platinum sensitive disease.
g. To ascertain the efficacy and safety of bevacizumab in combination with chemotherapy in the treatment of recurrent, platinum resistant disease.
h.To determine if treatment with paclitaxel plus the angiopoietin inhibitor AMG 386 is superior to paclitaxel alone in patients with recurrent, partially platinum sensitive or platinum resistant disease.
i.To determine if treatment with liposomal doxorubicin plus the AMG 386 is superior to liposomal doxorubicin alone in patients with recurrent, partially platinum sensitive or platinum resistant disease.

each). Median PFS was 5.2 with median OS still awaited at present. On the basis of these data, the role of cediranib in combination with standard chemotherapy in platinum sensitive first recurrence is being explored as part of the MRC ICON6 trial.[20] This trial also seeks to evaluate any benefit that may be added by using cediranib as a maintenance therapy following chemotherapy. It is important to note that the starting dose of cediranib has been reduced to 20mg/day to attempt to improve the safety profile of this combination.

Intedanib

Intedanib, BIBF 1120, is an oral TKI, which targets VEGFR, platelet derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR). It has been tested in the Phase II setting as maintenance monotherapy following at least second line chemotherapy for ovarian cancer.[21] Eighty-three patients were randomised to receive continuous intedanib 250mg twice a day or placebo for up to nine months, with the primary endpoint of PFS at 36 weeks. The 36-week PFS rates were 16.3% for BIBF 1120 and 5.0% for placebo with a hazard ratio of 0.65 (95% CI, 0.42 to 1.02; P = 0.06). There was no statistical difference in grade 3 or 4 toxicities between the groups, with 34.9% of the treatment arm having a grade 3 or 4 toxicity compared with 27.5% in the placebo arm. There was a higher incidence of grade 3 or 4 hepatotoxicity in patients with BIBF 1120 (51.2%) compared with patients on placebo (7.5%; P < 0.001) but this was rarely considered clinically significant. The Phase II trial was not powered for a direct comparison of efficacy between the two arms but these results have provided the basis for a large Phase III study, AGO-OVAR 12.[22] This trial is designed to investigate the efficacy of intedanib in combination with carboplatin and paclitaxel chemotherapy followed by maintenance treatment as first line therapy for advanced epithelial ovarian cancer.

Pazopanib

Pazopanib is an oral agent that targets VEGFR1-3, PDGFR and c-kit. The use of pazopanib as maintenance therapy after chemotherapy has been assessed in asymptomatic patients with recurrent epithelial ovarian cancer who had GCIG-defined CA125 progression and small volume disease.[23] Thirty-six women were enrolled and were given oral pazopanib 800mg once a day (od) until the detection of unacceptable toxicity or disease progression. Thirty-one percent of patients reached the primary endpoint of GCIG-defined CA125 response. The median duration of CA125 response was 113 days. The drug was generally well tolerated with the most common adverse events leading to discontinuation being grade 3 ALT (8%) and AST (8%) elevation. Only one grade 4 toxicity (peripheral oedema) was reported. Following these results, a randomised Phase III trial (AGO-OVAR 16)[24] has been designed to further investigate the efficacy and safety of pazopanib as maintenance therapy in patients following first line chemotherapy for epithelial ovarian cancer.

Sunitinib

Sunitinib acts by targeting VEGFR, epithelial growth factor receptor (EGFR) PDGFRα, PDGFRβ and c-kit. Sunitinib monotherapy has been tested in the Phase II setting in patients with epithelial ovarian cancer recurring after first or second line chemotherapy.[25] The disease could be platinum-resistant or sensitive but had to be measurable for the patient to be deemed eligible. Initial dosing was 50mg od for four-week cycles, followed by a two-week break. This was altered to 37.5mg od continuous dosing following the observation that fluid accumulation occurred during treatment breaks. Responses to sunitinib treatment were modest and confined to the 50mg dose level, with an overall PFS of 4.1 months. Interestingly, the fluid accumulation may be due to the relatively rapid clearance of the drug when compared with the induced increase in plasma VEGF, leaving the latter to cause fluid accumulation when the drug was stopped. Another consideration is effect of PDGFRβ inhibition in these patients, as rapid fluid accumulation has been previously reported in a study of a pure PDGFRβ antibody in patients with ovarian and colorectal cancer.[26] It is clear from this trial that dose and scheduling are key considerations for any future studies using sunitinib in ovarian cancer.

Sorafenib

Sorafenib acts on multiple targets including RAF-1, VEGFR-2, EGFR-3, PDGFR-β, FLT-3 and c-kit. The role of sorafenib in the treatment of recurrent ovarian cancer has been explored in several Phase II studies and has demonstrated modest activity at the expense of significant toxicity. A recent Phase II trial of 73 patients evaluated the use of sorafenib 400mg bd monotherapy following relapse after one or two prior chemotherapy regimens. Median PFS was 2.1 months with a median OS of 16.3 months. The toxicities were considerable with grade 3 or 4 toxicities classified as follows: rash (n=7), hand-foot syndrome (n=9), metabolic events (n=10), gastrointestinal events (n=3), cardiovascular events (n=2) and pulmonary events (n=2).[27] Significant toxicities also led to the early closure of a Phase II trial of sorafenib 400mg bd in combination with carboplatin and paclitaxel in the neoadjuvant setting. Only four patients were enrolled into this trial due to unacceptable toxicity. Three of the four patients had life-threatening events in the form of cardiac failure, myocardial infarction and anastomotic leak.[28]

Aflibercept

Aflibercept is a fusion protein, containing the VEGF-binding domain of VEGFR-1 and VEGFR-2 fused to the Fc region of immunoglobulin G. It acts as a soluble decoy receptor and prevents binding of VEGF-A, VEGF-B and PlGF to their receptors.[29] Aflibercept 2 or 4mg/kg iv q2w has been shown to have single agent efficacy in a Phase II study of 215 patients with advanced epithelial ovarian cancer, following three or four lines of previous therapy.[30] This study reported a radiological response rate of 7.3% and a median PFS of 13.3 weeks using a dose of 4mg/kg. Interestingly, of the forty patients with evaluable ascites at baseline, 77.5% had stabilisation or reduction of their ascites. Further information from ongoing Phase II trials is awaited prior to decisions regarding the suitability of aflibercept for investigation in Phase III trials.

Angiopoietin Inhibition

The angiopoietins (Ang1 and Ang2) bind to the tyrosine kinase receptor Tie-2 on endothelial cells and act to regulate angiogenesis through endothelial integrity. Agents which inhibit angiopoietin are now in development. AMG 386 is an angiopoietin antagonist, peptide-Fc fusion protein that selectively binds Ang1 and Ang2 and prevents their interaction with the Tie2 receptor. Clinical activity was found in a Phase I trial[31] and this was further tested in a Phase II study of AMG 386 in combination with weekly paclitaxel in patients with recurrent ovarian cancer.[32] One hundred and sixty-one patients were randomised to receive weekly paclitaxel 80mg/m^2 (three weeks on/ one week off) plus weekly AMG 386 10mg/kg (Arm A) or weekly AMG 386 3mg/kg (Arm B) or placebo (Arm C) until unacceptable toxicity or disease progression. Median PFS in Arm A was 7.2 months; Arm B 5.7 months and Arm C 4.6 months but this difference was not statistically significant. Notable toxicities included peripheral oedema (≥ Gr3 Arm A 4%, Arm B 6%, Arm C 4%), hypokalaemia (≥ Gr3 Arm A 12%, Arm B 11%, Arm C 4%), thrombotic events (arterial ≥ Gr3 Arm A 2%, Arm B 2%, Arm C 0%; venous Arm A 6%, Arm B 6%, Arm C 9%) and hypertension (no episodes ≥ Gr3). Although the primary endpoint of PFS did not show a statistically significant improvement with the addition of the trial drug, activity was suggested by the secondary endpoint of CA125 response. The efficacy of AMG 386 will now be tested in combination with conventional chemotherapy regimens in patients with recurrent partially platinum sensitive or platinum resistant epithelial ovarian cancer as part of the Phase III TRINOVA studies.[33,34]

Discussion and Conclusion

Agents targeting the angiogenic pathways have shown promising activity in the treatment of ovarian cancer. Regulatory data from two Phase III trials (GOG218 and MRC ICON7) demonstrate that patients with advanced disease with bulk residual tissue have an improved PFS if treated with carboplatin, paclitaxel and bevacizumab. Follow-up of the pre-planned PFS analysis of high-risk patients in ICON7 has also shown an OS advantage. OS not been evaluated in GOG218. These data have two implications. If the high-risk population in ICON7 benefitted much more than the overall trial group, then the data point to a lack of benefit in early stage (adjuvant) disease. In other words, patients with early stage disease do not benefit from VEGF inhibitors. Secondly, and more contentiously, the optimum dose level is not clear. The OS advantage of ICON7 was seen in a subgroup analysis that was requested by regulatory authorities; the mature OS data will not be available until 2013. In addition it is quite possible that we will not see OS data from GOG218 since this PFS was the primary endpoint and the availability of bevacizumab in the US increases the probability that women will receive bevacizumab at some point in their illness. Thus, the two trials clearly show a PFS advantage for high stage, high-risk patients in the first line setting. The true clinical significance of the OS findings for high-risk patients in ICON7, and therefore the dose-level implications, remain obscure.

OCEANS demonstrated a PFS advantage in platinum-sensitive first recurrence of ovarian cancer that was of a similar magnitude to that seen in the first line setting, raising the question of whether VEGF inhibition should be confined to first line, second line or both lines of treatment. Clinical trials that address some of these issues are summarised in Table 4. However, we have seen for the first time in this disease, the development of effective maintenance therapy. Whether the addition of new anti-angiogenic agents, such as those that target angiopoietin or drugs that have shown activity in the maintenance therapy of serous ovarian cancer e.g. olaparib,[35] remains to be demonstrated. Nevertheless, these data demonstrated that angiogenesis appears to be a valid target in ovarian cancer.

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Cancer During Pregnancy: Interim Data from a Preclinical and Clinical Study

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Introduction

Cancer is the second leading cause of death in women during the reproductive years and complicates between 0.06% and 0.10% of all pregnancies.[1] In Europe, this number translates into 3000 to 5000 annual new cases of cancer diagnosis during pregnancy. As women in developed societies defer childbearing to the third or fourth decade of life, and the incidence of several malignancies rises with increasing age, this rare co-incidence is likely to become more common.

The treatment of cancer in pregnant women is a challenge since both the maternal and the foetal well-being need to be considered. Since the co-incidence of cancer during pregnancy is uncommon, clinical experience is rather limited and literature is restricted to case reports, small retrospective case series and reviews. In the absence of prospective studies related to cancer diagnosis and treatment during pregnancy, we initiated this study in 2005. In the first phase of this research, focus was put on the current management modalities and the maternal and foetal outcome. Furthermore, we initiated a pharmacological study addressing pharmacokinetics of chemotherapy in pregnant women and transplacental passage of these drugs. Finally, we investigated the effects of *in utero* exposure to chemotherapy on neurological development.

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Current Management Modalities and Maternal and Foetal Outcome[2]

In order to assess current treatment modalities and the impact on the obstetrical and neonatal outcome an international multicentric registration study was initiated in Belgium, the Netherlands and Czech Republic. Between 1998 and 2008, 215 patients with a diagnosis of cancer during pregnancy were registered. The most frequently encountered tumour types were breast cancer (46%), haematological (18%) and dermatological malignancies (10%). These are the same types of tumours seen in non-pregnant women of this age group. This observation confirms the idea that pregnancy itself is no risk factor.

In 5/215 (2.3%) patients a miscarriage occurred at 10.7 +/- 4.8 weeks of gestation, before cancer treatment was started. In 30/215 (14.0%) patients the pregnancy was terminated at a gestational age of 10.9 +/- 6.8 weeks. In 13 patients (43.3%) this occurred after 13 weeks gestational age. In 58/215 (27.0%) patients treatment was delayed till postpartum. Here, the cancer diagnosis was made at a gestational age of 30.6 +/- 9.4 weeks. In 122/215 (56.7%) patients a single or a combination of treatment modalities was initiated during pregnancy, after a cancer diagnosis at a gestational age of 19.6 +/- 8.5 weeks.

The mean gestational age at delivery was 36.2 +/- 2.9 weeks. 8.4% delivered before 32 weeks (n=15/179), 45.8% between 32 and 37 weeks of gestation (n=82/179), and 45.8% at term (>37 weeks) (n=82/179). So 54% of the children were born preterm, with subsequently a high admission rate to the neonatal care unit. In the vast majority (90%) the delivery was induced. The complications of preterm birth are well studied and include a.o. intraventricular haemorrage, bradycardia/apnoea, need for respiratory assistance, necrotising enterocolitis, sepsis, seizures,

hypoglycaemia and feeding problems. Recently Bastek *et al.* showed that also late preterm neonates (34-37 weeks) have significantly more medical complications compared to their term counterparts.[3] Besides these immediate effects, preterm birth is also associated with long term morbidities and impaired cognitive and behavioural outcomes.[4] We believe that the consequences of preterm delivery in our study population are underestimated. Also in an oncological setting the prevention of prematurity deserves full attention. Prevention of prematurity can be realised either by postponing or by continuing treatment until a term delivery can be obtained. Deliberate delay of therapy to achieve foetal maturity appears to be a safe option for patients with early-stage disease. Continuation of the treatment that was started during pregnancy is a second way to prevent prematurity. To date treatment during pregnancy is continued until foetal viability is reached. Instead, foetal maturity should be the preferred criterion to induce labour. In a multidisciplinary setting, a maximal effort should be executed to delay the delivery till at least 35-37 weeks.

Furthermore, our data show no increased incidence of congenital malformations after *in utero* exposure to chemotherapy. These observations confirm the evidence that cytotoxic treatment administered after the first trimester of pregnancy does not result in a higher incidence of congenital malformations.[5-6]

Foetal growth restriction is a permanent concern when cancer is treated during pregnancy,[5,7-8] and was confirmed by the findings in the current study. In 26/175 cases the birth weight was below the 10th percentile for gestational age (14.9%, binomial test, p=0.054). The low birth weight cases were not correlated with a certain type of cancer, but the largest proportion of small for gestational age children was seen in patients with haematological tumours (9/33, 27.3%). Binomial testing revealed a significant increase of small for gestational age children in the group receiving treatment during pregnancy (surgery, chemotherapy or radiotherapy) (n=21/117 (17.9%). In mothers receiving chemotherapy and/or radiotherapy, small for gestational age babies were seen in 16/66 (24.2%, binomial test p=0.001), compared to 10/109 (9.2%) in the pregnancies without cytotoxic treatment (binomial test, p=1.320). Whether the effect on foetal growth is determined by the maternal illness which is associated with malnutrition and a catabolic status,[9] or by direct or indirect effects of the treatment remains an unanswered question.

In conclusion, the study shows an overall good outcome of pregnancies complicated with cancer. However, a high rate of preterm inductions with a subsequent high rate of admissions to the neonatal care unit was observed. Interdisciplinary decision making on the timing of delivery, with obstetricians and neonatologists, is necessary. Preferably, delivery should not be induced before 35-37 weeks. Current data confirm that cytotoxic treatment, administered during the second and third trimester of pregnancy, does not increase the rate of congenital malformations.[2]

Pharmacokinetics of Chemotherapy during Pregnancy

In the second part, we address the pharmacokinetics and transplacental passage of chemotherapy during pregnancy. Current information is based on theoretical inferences from the physicochemical characteristics of drugs, physiologic adaptations in pregnancy and the general distribution behaviour of drugs. The use of an animal model was necessary since certain experiments would be ethically unjustified to perform in humans.

Transplacental Passage of Chemotherapy

In a first phase transplacental transfer of cytotoxic agents was studied in a mouse model. Ninety minutes after IV drug injection, maternal and foetal blood samples were collected simultaneously. Plasma drug levels were determined using high performance liquid chromatography (HPLC) or atomic absorption spectrometry (AAS). Foetal plasma concentrations of doxorubicin, epirubicin and daunorubicin were 5.1 +/- 0.6%, 4.8 +/- 3.8%, 13.3 +/- 3.5% (mean +/- SD) of the maternal concentrations, respectively. For vinblastine and cytarabine foetal plasma concentrations were 13.8 +/- 5.8% and 56.7 +/- 22.6% of the maternal concentrations, respectively. Carboplatin integrally passed the mouse placenta (117.0 +/- 38.9%). Paclitaxel could not be detected in foetal plasma. These results show a high variability in foetal exposure between the different agents. Albeit, except for carboplatin, all foetal drug levels were much lower than maternal plasma levels.[10]

Although these results were reassuring, important limitations of these experiments must be taken into account: only one drug could be administered, while in clinical practice combination therapy is frequently used, and the rodent placenta differs importantly from that of humans. In order to achieve results that could more reliably be extrapolated to the human setting, an adequate model with a close phylogenetic relationship with humans was searched for. This model had to harbour a sufficient similarity with humans with respect to embryological development, placental structure and function, reproductive physiology and endocrinology, and drug metabolism. First, the baboon model was shown to address these requirements.[11] Subsequently, transplacental passage of chemotherapeutics used in clinical practice for the treatment of breast cancer, cervical cancer and haematological malignancies, was studied in a baboon model.

The administered regimens were the following: 5-fluorouracil-epirubicin-cyclophosphamide (FEC) was in normal (100%) dosage (n=2), FEC 200% (n=1), doxorubicin-bleomycin-vinblastine-dacarbazine (ABVD) 100% (n=5), ABVD 200% (n=1), docetaxel-trastuzumab (n=1), paclitaxel (n=2), docetaxel (n=2), paclitaxel-carboplatin at normal (n=2) and at 50% dosage (n=1) and docetaxel-carboplatin (n=1). At predefined time points over the first 76 hours after the start of the drug infusion, foetal and maternal blood samples, amniotic fluid (AF) and maternal urine were collected simultaneously. Foetal and maternal tissues were collected during necropsy. HPLC, liquid chromatography-mass spectrometry (LC-MS), enzyme-linked immunosorbent assay and

AAS were used for bio-analysis of doxorubicin, epirubicin, vinblastine, cyclophosphamide and (4-hydroxy-) cyclophosphamide, trastuzumab, docetaxel, paclitaxel and platin.[12-13]

Doxorubicin and Epirubicin

Less than 10% of maternal concentrations of doxorubicin and epirubicin was encountered in the foetal compartment in a baboon model, which suits the expectations based on molecular properties, namely a high molecular weight (527g/mol) and protein binding (50-85%).[14] Moreover these drugs are substrates to ABC-transporters like P-gp, an efflux transporter for various xenobiotics which is expressed on bile canaliculi, but which is also present in the placenta[15] and might explain the limited transplacental transfer of these anthracyclines. The transfer rate in the baboon was consistent in blood and tissues and paralleled passage rates in mice. The low transplacental transfer of doxorubicin and epirubicin is reassuring with regard to foetal toxicity and long term effects. However, the unknown susceptibility of the foetal tissues to even low cytotoxic drug concentrations needs to be further explored. In particular, the foetal heart may be sensitive since anthracyclines induce a dose-related cardiotoxicity.[16] To date, case series do not show impaired heart function or morphology in children after prenatal exposure to anthracycline-based chemotherapy.[17-18] The low levels of anthracyclines in the foetal heart may contribute to a favourable cardiac outcome in the offspring.

Vinblastine

Vinblastine is highly protein bound (99%), has a high molecular weight (811g/mol) and is a substrate of ABC-transporters like P-gp and MRP. These drug properties contribute to a low transplacental transfer, 18.5 +/- 15.5% (n=9), that was shown in the baboon study.[12]

Cyclophosphamide (CP)

CP is an inactive prodrug that is converted by hepatic microsomal enzymes to reactive intermediates, of which 4-OHCP is the most important one. Plasma protein binding of CP is low (12-14%) resulting in easy penetration of most membranes.[14] Therefore it was assumed CP would readily pass the human placenta.[19] On the other hand, 4-OHCP is bound more tightly to plasma protein (50%), and the placental diffusion rate in mice was lower than for CP.[20] Results from our baboon study indeed showed a complete transplacental passage of CP (100%). The 4-OH metabolite was detected in much lower concentrations in the foetus (25.1 +/- 6.3% (n=3)).[12] This can be explained by the reduced or absent oxidative metabolism capacity of the foetus for CP that will limit the conversion of the inactive parent compound to the active 4-OH metabolite. Moreover, maternal 4-OHCP is more strongly bound to plasma proteins thus reducing transplacental transfer.

It appears that the foetal exposure to the active metabolite of CP is limited, however, further research is indicated taking into account the late effects of cyclophosphamide on induction of secondary neoplasms (bladder cancer, leukaemias) and its detrimental impact on gonadal function in young adults.

Carboplatin

We determined a carboplatin materno-foetal transfer of 57.5 +/- 14.2% (n=7).[13] Carboplatin is known to be bound to plasma proteins only for 24-50%.[14] The high free drug fraction and relative low molecular weight (371 g/mol) explain the substantial tranplacental passage.

Paclitaxel and Docetaxel

Comparison of foetal and maternal plasma levels of paclitaxel and docetaxel revealed a very low placental passage. The concentration of paclitaxel measured in foetal plasma was 1.4 +/- 0.8% of maternal concentrations (n=7). Docetaxel could not be detected in foetal blood samples (n=9). However, measurements in foetal and maternal tissues showed a delayed, but important distribution of taxanes into the foetal compartment.[13]

Paclitaxel and docetaxel have a high molecular weight (854 and 862 g/mol), are highly lipid soluble, exhibit a wide tissue distribution, are highly protein bound (>80-90%) and consequently, have a long half-life. Furthermore, taxanes are substrates of ABC transporters like P-gp and MRP. These active transporters are also present in the human placenta and protect the foetus against toxic xenobiotics.[15] These molecular characteristics of taxanes explain the fast distribution, the relatively low plasma levels and the slow elimination. The foetus appears to act as a 'deep' compartment, where drugs are stored till maternal plasma concentrations decrease again. Taxanes are extensively metabolised in the liver by the cytochrome P450 isoenzymes, CYP2C8 and CYP3A4 (paclitaxel) and CYP3A4/5 (docetaxel). The maturation of these cytochromes mostly occurs in the first weeks of neonatal life.[15] Therefore, it can be assumed that foetuses are unable to metabolize taxanes and remain susceptible to their cytotoxic effects. The implication of the storage of taxanes in foetal tissues is not yet clear.

Trastuzumab

Trastuzumab is a humanised monoclonal antibody targeting HER2-positive breast cancer cells. The major side effect of trastuzumab is cardiotoxicity. Trastuzumab is also associated with oligohydramnion when administered during pregnancy. In a baboon model, 2 hour and 26 hour after trastuzumab infusion, respectively 85% and 3% of the maternal plasma concentration was found in the foetal plasma.

Foetal tissue concentrations, including the heart, varied between 5% and 14% of the maternal concentration.[13] The lack of a mature reabsorption function of the foetal kidney results in relative high

concentrations of trastuzumab in amniotic fluid. Trastuzumab induced oligohydramnion might be related to HER2 inhibition in foetal nephrogenic cells and decreased foetal renal blood flow by VEGF inhibition. These results add to the knowledge that trastuzumab is associated with oligohydramnion. Foetal cardiotoxicity after *in utero* exposure to trastuzumab deserves further attention. Children *in utero* exposed to trastuzumab are candidates for nephrologic and cardiologic follow-up.

For a correct interpretation of results on plasma concentrations, it should be kept in mind that it is only the free drug fraction and not the protein bound fraction that is active, or toxic for the foetus. The plasma protein levels measured in foetal and maternal baboon plasma are comparable to the levels and the pattern of evolution seen in human pregnancies.[21-22] Foetal plasma protein levels are lower than in adults, but are increasing near term. This difference is relevant in drugs with a strong protein binding, including anthracyclines (50-85%) and vinblastine (>99%). It can be assumed that earlier in pregnancy, a higher proportion of the foetal drug concentration is free and therefore more toxic.

Pharmacokinetics of Chemotherapy in Pregnant Women

Next to the potential toxicity of chemotherapeutics on the foetus, also maternal effects were studied. Most anticancer drugs exhibit a narrow therapeutic window with small margins between toxic and therapeutic exposure. Inter-individual pharmacokinetic and pharmacodynamic variabilities are usually substantial and may be augmented by pregnancy.[23] During pregnancy multiple changes in physiology occur affecting the major pharmacokinetic processes of a drug: absorption, distribution, metabolism and excretion (ADME).[24] This may have therapeutic and toxic consequences for both the pregnant woman and the foetus. Due to ADME changes, the pregnant patient may be exposed to subtherapeutic or toxic drug levels. Obviously, these situations should be prevented, particularly in oncology where patients are treated with strong acting, mutagenic and teratogenic chemotherapeutics.

During pregnancy an increase in progesterone level is believed to be responsible for a delayed gastrointestinal motility and increased transit time, altering the drug absorption and entero-hepatic circulation resulting in lower peak levels but increased exposure. The volume of distribution of drugs may be altered during pregnancy as a result of the increase in fat stores as well as extracellular fluid volume and a plasma volume expansion by 50%. As a result of this volume expansion, a decrease in the (peak) serum concentration of many drugs has been documented.[25] Furthermore, the amniotic fluid may serve as a third space for water soluble drugs, like methotrexate or mitoxantrone, with prolonged exposure and delayed elimination resulting in both maternal and potentially foetal toxicity.[19]

As the pregnancy advances, the rate of plasma volume expand exceeds the rate of albumin production, creating physiological dilutional hypoalbuminaemia. Moreover, steroid and placental hormones occupy protein binding sites, thus decreasing the protein binding of drugs. The overall effect is a decrease in binding capacity for albumin, and therefore, an increase in unbound drug. However, as more free drug is available for either hepatic biotransformation or renal excretion, the overall effect is an unaltered free drug concentration.[25]

The increased hepatic blood flow will lead to higher metabolic rates. Moreover, the increased secretion of oestrogen and progesterone in normal pregnancy affects hepatic drug metabolism in different ways: a higher rate of hepatic metabolism of certain drugs, such as phenytoin, is possibly a result of stimulated hepatic microsomal enzyme activity induced by progesterone. On the other hand, the hepatic elimination of other drugs, such as theophylline and caffeine, is reduced secondary to competitive inhibition of microsomal oxidases by progesterone and estradiol. These hepatic alterations might be detrimental for drugs that need to be metabolised to become active, like cyclophosphamide, or vice versa, for drugs that need to be metabolised to become inactive. Finally, the cholestatic effect of oestrogen may interfere with the clearance of drugs, which are secreted in the biliary system.

As renal plasma flow increases by 25-75% and glomerular filtration rate by 50%, renally cleared drugs demonstrate enhanced elimination and lower steady-state serum concentrations.[25]

The pharmacodynamic (anti-tumour activity and toxicity in relation to the dose administered) consequences of all these physiological changes for chemotherapeutic agents are difficult to predict without pharmacokinetic data. Therefore, it is still unknown whether the pregnant patient is treated optimally with standard chemotherapy regimens as applied in current clinical practice.[5,19] To answer this crucial question, we initiated a study on the pharmacokinetic behaviour of chemotherapeutic agents, comparing the pharmacokinetic parameters in pregnant and nonpregnant patients.

In a baboon study and a clinical study we analysed pharmacokinetic parameters of chemotherapeutics in pregnant and nonpregnant state.[26] To this end standard-dosed chemotherapy regimens were administered in pregnant and nonpregnant baboons/women, followed by serial blood samplings. Drug plasma levels were determined using high-performance-liquid-chromatography and atomic-absorption-spectrometry. A non-compartmental pharmacokinetic analysis with the determination of C_{max}, AUC, $t_{1/2}$, clearance and distribution volume was performed using WinNonLin Software.

In a pregnant baboon model we assessed the pharmacokinetic characteristics of doxorubicin, paclitaxel and platinum during and after

pregnancy. For the three drugs, a decrease in plasma drug exposure (AUC-D and C_{max}-D) and an increase in clearance and distribution volume was seen during pregnancy.

In the clinical trial intraindividual comparative data were obtained in two patients exposed to doxorubicin and one patient receiving paclitaxel/platinum during and after pregnancy. Subsequently, we performed a pooled analysis on 16 cycles from pregnant patients and 11 from nonpregnant patients. Numbers of pregnant/nonpregnant patients were 5/2, 7/5, 4/4 and 2/2 for paclitaxel, doxorubicin, epirubicin and platinum, respectively. For all drugs tested, a decreased area under the curve and maximal plasma concentration and an increased distribution volume and clearance were observed during pregnancy (Table 1).

The results of the three studies are consistent, confirming the hypothesis that gestational physiologic changes alter the pharmacokinetic patterns of cytotoxic drugs. AUC-D and C_{max}-D are lower during pregnancy due to an increase in clearance and distribution volume. These data clearly indicate that follow-up of mothers who received chemotherapy during pregnancy is warranted.

Effects of Prenatal Exposure to Chemotherapy on the Neurological Outcome

During the second and third trimester of pregnancy, administration of chemotherapy is considered relatively safe on the short-term.[2,5] However, reliable data on the long-term outcome of children after prenatal exposure to chemotherapy are lacking. Foetal organogenesis ends around eight weeks after conception for most organs, except for the brain and gonads. Consequently, questions rise on the possible long-term effects of prenatal exposure of chemotherapy on the neurological development, the fertility and carcinogenesis in these children.[5,27,28]

To date, available data on long-term follow-up of the children are poor. Only two series have been described with a follow-up till school-age. Albeit, the applied methodology was described poorly or results were biased by paternal opinion.[29-30]

Aviles *et al.* described a series of 84 children from mothers with haematological malignancies who received chemotherapy during pregnancy. The children were examined for physical health, growth, general development and haematological, cytogenetic, neurological, psychological and learning disorders. However, no details on neurological and psychological tests were provided. They reported all children, including 12 second-generation children, had a normal birth weight, a normal learning and educational performance, and no congenital, neurological or psychological abnormalities were observed. With a median follow-up of 18.7 years (range, 6-29 years), no malignancy has been observed.[29] Nevertheless, with this reassuring result, questions rise, as in a general population group of 96 children it is expected to see at least some problems.

Hahn *et al.* reported on the outcome of 40 children (age 2-157 months) after *in utero* exposure to chemotherapy for breast cancer. The parents and teachers of the children were asked to participate in a telephone/mail survey on the development and health of the children. In this series, 2 out of 18 school-going children were reported to have special educational needs. In 43% of children no medical problems were reported. Problems registered in the remaining cases were mainly allergy, eczema, asthma and upper airway infections.[30]

Study of Brain Development and Behaviour of the Offspring after Vinblastine and Doxorubicin Administration to Pregnant Mice

Searching for the target areas of potential neurological damage, we performed a preclinical study with both morphological and functional examination of the offspring in a mouse model.[31] Different dosages of doxorubicin, vinblastine or saline were administered to pregnant C57BL/6J mouse dams on gestational day 17.5. Both immediate (24h p.i.) and residual (4-5 months p.i.) brain damage were investigated by light- and electron microscopy, and a battery of behavioural tests was performed in three month-old offspring.

Exposure of high dosages of doxorubicin and vinblastine caused transient regionally limited lesions to brain microvasculature and surrounding parenchyma and an inconsistent development of cortical ectopias resembling microgyri and isolated lissencephaly type 2–like overmigrations. These lesions could not be detected in three month old mice, suggesting absence of permanent morphologic damage.

Functional testing of drug exposed mice offspring indicated few subtle, but specific alterations in their neurobehavioural profile. No learning impairment was consistently observed, but several tests indicated changes in emotional behaviour and increased anxiety in the drug exposed mice.

We concluded that a thorough morphological neurological assessment revealed subtle changes in the brain. This underscores the need for long-term follow-up with a special emphasis on the neurological outcome.

Clinical Study

In the absence of standardised follow-up data of children *in utero* exposed to chemotherapy, we initiated a prospective multicentric international study (University Hospital Gasthuisberg Leuven, St Radboud Hospital Nijmegen and Motol University Hospital Prague). The strength of this study lies in its robustness: all children are clinically examined with subsequent determination of the Bayley score at 18

	Paclitaxel		Carboplatin		Doxorubicin		Epirubicin	
	Pregnant (n=5)	Control (n=2)	Pregnant (n=2)	Control (n=2)	Pregnant (n=7)	Control (n=5)	Pregnant (n=4)	Control (n=4)
Age (year)	32.0 +/- 4.7	31.0 +/- 4.2	31.0 +/- 4.2	31.0 +/- 4.2	32.0 +/- 2.8	33.4 +/- 13.2	36.3 +/- 2.9	36.3 +/- 8.1
GA (weeks)	26.2 +/- 3.6	-	24.0 +/- 1.4	-	29.0 +/- 3.8	-	28.0 +/- 6.1	-
BSA (m^2)	1.8 +/- 0.1	1.8 +/- 0.1	1.9 +/- 0.2	1.8 +/- 0.1	1.9 +/- 0.2	1.8 +/- 0.2	2.0 +/- 0.2	1.6 +/- 0.1
Vd (l)	862.1 +/- 518.9	513.4 +/- 34.2	378.8 +/- 76.4	272.7 +/- 1.3	2486.3 +/- 656.8	1915.3 +/- 317.6	2710.4 +/- 325.6	2236.0 +/- 493.1
$t_{1/2}$ (h)	16.7 +/- 8.4	12.5 +/- 2.0	23.7 +/- 8.6	28.9 +/- 9.9	25.6 +/- 7.7	25.5 +/- 5.6	19.4 +/- 3.4	22.8 +/- 5.9
Clearance (l/h)	34.7 +/- 4.3	28.7 +/- 2.7	11.4 +/- 1.9	6.9 +/- 2.3	68.6 +/- 9.4	54.1 +/- 13.7	98.0 +/- 11.6*	68.7 +/- 7.4*
Cmax- D*IT (ng/ml/mg*h)	21.8 +/- 7.1	39.8 +/- 2.3	7.6 +/- 4.3	11.9 +/- 1.7	5.9 +/- 2.4*	8.9 +/- 1.2*	5.1 +/- 1.4*	8.5 +/- 1.2*
AUC-D (h*ng/ml/mg)	29.2 +/- 3.7	35.1 +/- 3.3	88.9 +/- 14.9	152.7 +/- 51.4	14.9 +/- 2.3	19.7 +/- 6.3	10.3 +/- 1.2*	14.2 +/- 0.8*

Table 1. Pooled analysis of pharmacokinetic parameters of paclitaxel, carboplatin, doxorubicin and epirubicin in pregnant and control patients (Van Calsteren *et al*., 2010d). ** significant difference between pregnant and nonpregnant patients: p<0.05 (Wilcoxon Rank Sum test); GA, gestational age; BSA, body surface area; Vd, distribution volume; $t_{1/2}$, terminal half life; C_{max}-D*IT, maximal plasma concentration corrected for dose and infusion time; AUC-D, area under the curve corrected for dose.*

months, and a battery of neuropsychological tests focusing on working memory and attention at the ages of 5-6 year, 8-9 year, 11-12 year and 14-15 year. This study is currently ongoing.

Summary and Conclusion

The results obtained in this study suggest that *in utero* exposure to chemotherapy does not add to a worse neonatal outcome. This finding is explained by the fact that chemotherapy is not administered during the most vulnerable period of gestation (first trimester). Also the placental barrier-function protects the foetus from the toxic effects of chemotherapy and contributes to the reassuring findings in the children. Before major conclusions can be drawn, more children should be followed and a longer period of follow-up is required. Plasma chemotherapy exposure is lower during pregnancy than in nonpregnant women. Further research is required to test whether these alterations also include a lower tumour toxicity of chemotherapeutic agents, which is necessary to evaluate whether pregnant women receive optimal chemotherapy treatment. Therefore, this research project is continued and further elaborated nationally and internationally.

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Upcoming Congresses and Meetings

5th International IVI Congress: Reproductive Medicine and Beyond

04-06 April, 2013

Sevilla, Spain

The aim of this congress is to continue providing top-level reproductive medicine congresses, addressing cutting edge topics in this continuously evolving field of human reproduction and offering the most reputable international speakers available.

British Maternal And Fetal Medicine Society 16th Annual Conference (BMFM 2013)

25-26 April, 2013

Dublin, Ireland

Topics at this year's conference will be diverse as 'The use of microarray technologies for karyotyping in prenatal diagnosis', 'Perinatal outcomes in the small for gestational age fetus with 'normal' fetal Doppler studies', 'The effects of anticonvulsant medication on pregnancy', 'Vitamin D and adverse pregnancy outcomes', 'The use of syntocinon to augment the progress of labour' and 'The role of ultrasound in reducing maternal and perinatal mortality and morbidity'. Other programme highlights will be a lunch time symposium in collaboration with SANDS on 'Stillbirth - can it be prevented?' and a lunchtime symposium on 'Ultrasound of the fetal brain' sponsored by GE Healthcare.

XI Annual Meeting of the Mediterranean Society for Reproductive Medicine (MSRM)

02-04 May, 2013

Marrakech, Morocco

10 years ago the society was born in Taormina (Italy) with the aim to create a group dedicated to the study of all aspects of reproductive medicine and the promotion of science and research in all aspects of human reproduction. This remains their primary goal. This year's meeting will be held in the beautiful city of Marrakech.

First Global Conference on Contraception, Reproductive and Sexual Health

22-25 May, 2013

Copenhagen, Denmark

The 2013 conference will be a dynamic meeting with exciting scientific and social interactions with professionals from all over the world! Focusing on empowering of women and all aspects of sexual and reproductive health. An international Council representing professional organisations as well as individual opinion leaders will together with the ESC Scientific Committee ensure a high educational and scientific level with clear clinical translation. 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.

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

30 May-02 June, 2013

Istanbul, Turkey

The BCGIP (COGI) World Congress will provide a unique platform for world leaders and participants to conduct a vibrant discussion aimed at reaching consensus in the various fields of gynaecology. Debates, discussions and plenary lectures will facilitate this academic dialogue which will raise the most dynamic and challenging clinical and technological questions. The Congress will promote excellence in the fields of Gynaecology, 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.

Second International Conference on Triple Negative Breast Cancer

26-28 June, 2013

London, UK

Improving the limited treatment options and poor prognosis of patients with triple negative disease is a high priority for breakthrough. This conference will provide a comprehensive look at the challenges, controversies and breakthroughs in this disease, helping to provide patients with improved outcomes in future. This conference builds on the successful conference held in 2011 and will highlight novel laboratory approaches, innovative pre-clinical science and the latest clinical trial results. The aim is to discuss and advance our understanding of the aetiology, diagnosis and treatment of this challenging disease. The 3 day programme covers all aspects of triple negative disease

with invited plenary speakers and proffered abstracts presented as short talks or posters. We aim to create a workshop atmosphere with ample opportunity for discussion and sharing expertise across disciplines.

18th World Congress on Controversies in Obstetrics, Gynecology & Infertility (COGI)

24-27 October, 2013

Vienna, Austria

The groundbreaking series of COGI Congresses provide a unique platform to discuss controversial issues in all fields of Obstetrics, Gynaecology and Infertility. The ability to discuss only controversial topics with emphasis on clinical solutions in cases where no agreed-upon answers or consensus exist, provides clinicians with an insight and a take-home message that ameliorates treatment in the most difficult situations.

IVF Worldwide Live Congress

31 October-02 November, 2013

Berlin, Germany

The IVF Worldwide Live Congress is designed to explore the relations between IVF clinics and this emerging business technology. IVF-Worldwide Live will specifically focus on; collaboration between practitioners, researchers, IVF teams, and IVF patients and the industry, managing the on-line presence involves more than just creating a website, what patients find when they "Google" you affects the success of your practice. Participating in the congress will enable IVF teams to learn about how to use the internet to promote their clinics, to attract more patients, to dialog with patients over the web, to reduce workload and to improve the management performance and patient satisfaction by using new technology, leading us into becoming more effective health providers and business owners.

3rd World Congress of The International Society for Fertility Preservation ISFP

07-09 November, 2013

Valencia, Spain

The International Society for Fertility Preservation is founded upon the guiding principles of integrity and diversity of all international societies. Its role is leading and promoting progress in fertility preservation by international cooperation and collaboration. The ISFP is dedicated to scientific innovation and advances in medical care in the field of fertility preservation. Fertility preservation is a substantial quality of life issue for young cancer survivors. As a consequence, the demand for fertility preservation has dramatically increased. The aim of the Congress is to update current scientific and clinical development of fertility preservation strategies. This year's congress will be held in the beautiful Spanish city of Valencia.

Ovarian Club III The Inverse Pyramid: Regulating Follicle Number and Oocyte Quality

14-17 November, 2013

Paris, France

The Ovarian Club is a comprehensive forum where international experts share and discuss state-of-the-art management topics in order to pursue the optimal treatment for patients. The Ovarian Club enables researchers to present their new studies and findings in their fields of expertise in an interactive platform for discussions with the leading expert attendees.Previous Ovarian Club meetings, which dealt with the oocyte and the fertilisation process, were engaging and highly successful. Thus year's meeting in Paris, promises to be an exciting experience.

5th Asia Pacific Congress on Building Consensus out of Controversies in Gynecology, Infertility and Perinatology (BCGIP-COGI)

21-24 November, 2013

Shanghai, China

The 5th Asia Pacific BCGIP Congress will provide a unique platform for world leaders and participants to conduct a vibrant discussion aimed at reaching consensus in the fields of gynaecology, perinatology and infertility. The Congress will promote excellence in the fields of Gynaecology, 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. Not only will this be an exciting scientific event, it will also be held in the equally exciting city of Shanghai. Shanghai is full of rich history, vast cultures and a rich blend of religious heritage.

XXI World Congress of The International Federation of Gynecology and Obstetrics (FIGO)

04-09 October, 2015

Vancouver, Canada

Every three years since FIGO's founding in 1954, thousands of gynaecologists and obstetricians gather in one city to spend a week analysing and discussing new medical discoveries and looking at problems and issues that can be addressed by the application of low-cost techniques. The site for the World Congress rotates between the Africa-Eastern Mediterranean, Asia-Oceania, Europe, Latin America and North America regions of FIGO. The site is selected six years in advance by a majority vote at the General Assembly.

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