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OBSTETRICS & GYNAECOLOGY 2016

EXPERT GUIDE

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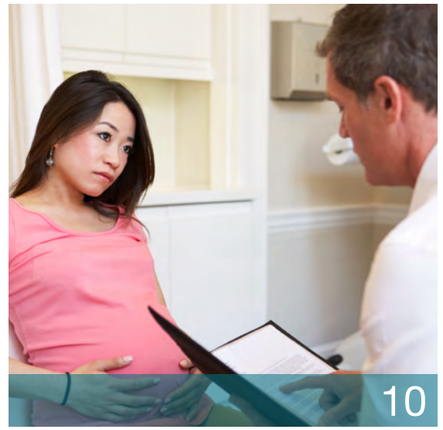

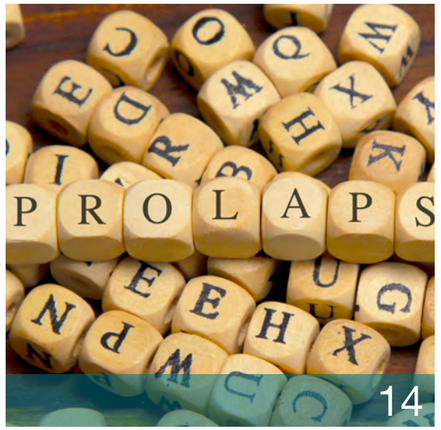

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Introduction

Science and medicine is developing at phenomenal speed. It is possible to detect chromosomal anomalies such as Down syndrome and Patau syndrome in early embryos through preimplantation genetic screening (PGS). Experts have identified ectopic pregnancy as one of the leading contributions to maternal mortality and have implemented measures in which to minimise risk. There is also greater information available to patients regarding common issues such as pelvic organ prolapse (POP) which affects up to 1 in 3 women. This Expert Guide highlights the aforementioned developments whilst also discussing other industry concerns such as addressing communication and language barriers for non-English speaking pregnant women in the UK and egg donation law using Israel as a case study.

Aside from industry trends there are also plenty of health concerns facing professionals within the obstetrics and gynaecology profession. In 2016, environmental fears, obesity studies and new diagnosis methods dominated the field, and birth rates have continued to drop to new record levels. Birth rates in the UK stayed the same from 2015 to 2016 at 1.89 births per woman, but international birth rates have continued to slow overall, following the trend since the birth rate highs of the early 1990s. Even birth rates in countries with traditionally high figures such as India and Bangladesh are lower too.

Links to chemicals in the air, water, food and products in the western world have been linked to neurodevelopment disorders in children for the first time, in a Project TENDR study. Although a worrying study, it also highlights some of the ways that these issues can be reduced. Research this year also showed that obesity in mothers can affect the genetic pre-dispositions of generations of children towards being obese themselves. Although only proved in mice offspring, scientists believe a similar trend is likely to be observed in humans as well. Russian researchers this year have created a urine-based test that can help detect preeclampsia in women, allowing for an earlier diagnosis which can lead to less impact on the child.

Also this year, concerns over the Zika virus (which if contracted during pregnancy, can cause microcephaly and other brain malformations), were loud and fearful. An outbreak in the Americas, with the first non-travelling (did not contract it whilst on holiday) North American case confirmed in February 2016, has led to precautions being advised for pregnant women and sexually active males in higher risk areas. The virus is also being discussed in relation to the 2016 Summer Olympics held in Brazil's Rio de Janeiro. The University of Utah will be conducting a study on exposure and contraction rates amongst the nearly 1,000 strong team travelling to the high risk area.

Global

OBSTETRICS & GYNAECOLOGY SNAPSHOT

131.4
million births per year

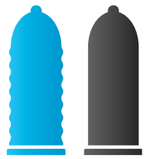
360,000
births per day

15,000
births each hour

250
births each minute[1]

- In **2012** the average global birth rate was **19.15** births per **1,000** total population
- Compared to **20.09** per **1,000** total population in **2007**[2]

- World population grew to **7.06 billion** in **mid-2012**
- **Developing countries** accounted for **97%** of this growth
- The **annual number of births** barely exceeds deaths
- By **2025**, it is likely that **deaths will exceed births** in the developed countries, the **first time** this will have happened in history.[3]



- Only **20%** of married women in sub-Saharan Africa use a modern form of family planning, the **lowest rate** in the world.
- Excluding China, **47%** of women in Asia use a **modern form of contraception**.
- Latin America **modern contraception**, at **67%**, rivals that of developed countries.
- Europe's population is projected to decrease from **740 million** to **732 million** by **2050** – due to low birth rates[4]
- About **one** in every **33** babies is born with a birth defect[5] (US)
- Every **4** **minutes**, a baby is born with a birth defect in the United States. That means nearly **120,000** babies are affected by birth defects each year[6]

Births per woman – averages TFR[7]

- Nigeria **seven** births per women
- Singapore **0.82** births per women

1. http://www.ecology.com/birth-death-rates/
2. https://en.wikipedia.org/wiki/Birth_rate
3. http://www.prb.org/publications/Datasheets/2012/world-population-data-sheet/fact-sheet-world-population.aspx
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America Obstetrics

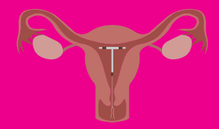
- **4 million** babies are born in the United States **each year**
- The U.S. fertility rate has been **declining** since **2007**
- The **most popular** day for babies to make their entrance in **2013** was **Tuesday**
- **Sunday** was the slowest day, with **33.3** fewer births than average
- In **2013** more new-borns arrived in **August** than in any other month

- Number of twin births: **135,336**
- Number of triplet births: **4,233**
- Number of quadruplet births: **246**
- Number of quintuplets and other higher order births: **47**[8]

Gynaecology

Five main types of cancer affect a woman's reproductive organs:

- **CERVICAL**
- **OVARIAN**
- **UTERINE**
- **VAGINAL**
- **VULVAR**



As a group, they are referred to as gynaecologic cancers.

- Overall, gynaecological cancers accounted for **9% of all reported cancers** in females in **2008**.
- The most commonly diagnosed was uterine cancer with **2,016 cases** in **2008**, followed by ovarian cancer (**1,272**), cervical cancer (**778**), vulval cancer (**282**), cancer of other female organ and placenta (**116**) and vaginal cancer (**70**).

5-Year relative survival rates	1982-1987	2006-2010
Ovarian cancer*	32%	43%
Uterine cancer	74%	82%
Cervical cancer	68%	71%[9]

- Men still dominate the field - about **64% of the doctors** practicing obstetrics and gynaecology are male
- Women have filled **70.3%** of the nation's ob-gyn residencies – soon it's likely that a majority of practising ob-gyn doctors will be female

America

It is estimated that 5 million women and girls of childbearing age in the U.S. have endometriosis.

- **Chlamydia** is the most frequently reported infectious disease in the U.S.
- However, **75%** of women have no symptoms and may not seek health care.
- Left untreated, **40%** of women will develop **PID** and many of these women will become infertile.
- In the U.S., more than **1 million** women experience an episode of acute **PID** each year, with teenagers having the **highest rate** of infection.

Europe

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Addressing the Issue of Communication & Language Barriers for Non-English Speaking Pregnant Women in the UK

By Dr. Natasha Abdul Aziz

Communication forms the backbone of the relationship between healthcare professionals and their patients. With an increasingly mobile global patient cohort – 25% of all pregnancies here occur in mothers born outside of the UK – healthcare providers need to consider not just which words to choose to identify, diagnose, and treat a woman, but also what language would best convey the situation as a whole, and offer support. William Osler reminded us that the difference between a good and great physician was that the latter treated patients, the former – just disease.

Whilst most hospitals have access to translators in person or over the telephone, the process can be cumbersome and impinge on patient privacy. Ad-hoc translators on the other hand are not trained in medical terminology and may have a relationship with the patient that renders their involvement inappropriate. Knowing whether your patient's concerns have been addressed and the information taken on board can be difficult to gauge without fluency in their native language. As George Bernard Shaw remarked, "the single biggest problem with communication is the illusion it has taken place".

That this illusion perpetuates can be seen in the stark statistics representing the past 10 years of maternity care, identifying women who are not native speakers of their host country's language to have a threefold higher morbidity and mortality rate.[1]

In 2011 The Centre for Maternal And Child Enquiries report listed professional interpretation services as a top 10 recommendation stating: "Professional interpretation services should be provided for all pregnant women who do not speak English. These women require access to independent interpretation services because they continue to be ill-served by the use of close family members or members of their own local community as interpreters. The presence of relatives, or others with whom they interact socially, inhibits the free two-way passage of crucial but sensitive information, particularly about their past medical or reproductive health history, intimate concerns and domestic abuse."[2]

The National Institute for Clinical Excellence found that 2/3 of pregnancy related morbidity and mortality was because "recent migrants… not proficient in English, did not readily access medical help and are particularly vulnerable"[3].

The latest *Mothers and Babies: Reducing Risk through Audit and Confidential Enquiry 2014* report found maternal mortality higher amongst migrant women, making up greater than 1/3 of all maternal deaths[4].

A review of the health of migrants in the UK conducted by the University of Oxford migration observatory in 2014 found "Barriers [to access, resulting in poor statistics] include inadequate information, particularly for new migrants unfamiliar with health care systems in the UK, insufficient support in interpreting and translating for people with limited English fluency… and cultural insensitivity of some front line health care providers (Phillimore et al. 2010; Johnson 2006). [These] cut across length of residence, affecting longer established migrants as well."[5]

With 4 million migrant women in the UK[6] – a quarter of whom lack proficiency in English –

"A study looking at the effectiveness of Google translate in converting 10 significant medical phrases into 26 languages resulted in only a 57.7% accuracy rate"

healthcare providers are recognising the value of sensitively using technology to assist them with communication. Whilst new live stream translating devices are being developed that hope to bring some semblance of *The Hitchhiker's Guide's* Babel fish to life, online computerised translations remain patchy at best. A study looking at the effectiveness of Google translate in converting 10 significant medical phrases into 26 languages resulted in only a 57.7% accuracy rate.[7]

The Kings Fund organisation – an independent charity that conducts research and analysis that can inform policy, for the betterment of healthcare in England – published an article this year looking at the technologies that will revolutionise healthcare delivery. At the top of their list – smartphones and mobile applications.[8] Examples of this include the winner of their grant money – an app aptly entitled New Natives – that is being designed to help vulnerable members of the population navigate healthcare service registration, in their own language. Last year's UN world summit award for mobile healthcare apps went to Universal doctor – and its offshoot Universal woman. It provides an offline language translation service with phrases previously professionally translated. Medibabble and Canopy developed across the pond offer a similar service for free.

Alongside the sad rise of the refugee crisis there has come a new wave of humanitarian technophiles, dedicated to developing translatable mobile resources. One such example is Techfugees – a volunteer collective that has run hackathons across the world to identify and build language and tech specific solutions to the problems of refugees. Empowerhack is an innovative collective that focuses on challenges specific to women accessing healthcare as refugees, and their mobile app *Hababy* (in production) aims to address those needs in a sensitive and language specific manner.

What these groups and others have identified is the paucity of quality information available on- and offline to non-English speaking women. However, while we continue to mold our clinical atmospheres to facilitate open communication between healthcare professionals and their patients, the Internet and Smartphone as a static, vetted, autonomously accessed resource, remains under-utilised. The majority of available patient information is in English, though because of the ease of posting opinion less than half of the websites reviewed in one study provided accurate information. This changed drastically when only NHS or government approved clinical websites were searched, with almost 80% providing clear and accurate answers to common questions posed.[9] We hope to contribute to this with an offering going live later this year (www.earlypregnancyservice.org), providing information regarding access to healthcare pathways, signposts to cultural and faith based organisations that provide support, and frequently asked questions in early pregnancy.

Ibn Sina (Avicenna) when speaking of the art and science of medicine said: "In truth every science has both a theoretical and practical side". Though the art of communication is infinitely nuanced, the medical and tech communities have come together to acknowledge the deficit of medical information to non-English speakers, and are addressing it through practical, pragmatic tools.

Natasha is a clinical research fellow in the Nuffield Dept. of Obstetrics & Gynaecology at the University of Oxford, and honorary registrar in obstetrics and gynaecology with the Oxford University Hospitals NHS Foundation Trust.

Her fellowship project to address the needs of vulnerable communities within the UK stemmed from her role as National Women's Health Lead with the Muslim Doctors Association in the UK – a community service group - and her volunteer work with NGO's. She acts as clinical advisor for Hababy and New Natives apps.

To access the website or its content for your organisation, or sponsor this endeavor please contact the author.

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Infiniti Healthcare

Pelvic organ prolapse (POP) – Embarrassingly common? – Help is out there

By Preetkiron Bhal

What is pelvic organ prolapse?
Any organ in the female body like the bowel, bladder, and womb can drop out of place. These result in a condition called pelvic organ prolapse (POP). If these organs are no longer in their normal positions and if this condition is not taken care of, quickly enough, these organs can fall farther into the vagina. POP is a very common condition which affects up to 1 in 3 women especially if they have had children.

The various types of POP which include cystocoele (prolapse of the bladder), hysterocoele (prolapse of the uterus), rectocoele (prolapse of the rectum), enterocoele (prolapse of small intestine), and vault prolapse (prolapse of the top of the vagina in women who have had a hysterectomy). Often more than one type of prolapse may occur at the same time.

What are the causes of POP?
The weakening of the vaginal support system results in this condition. There are several causes linked to POP. These include:

1. A lack of oestrogen (female hormone) following the menopause weakens the pelvic support structure that relies on this hormone for their strength.
2. Pregnancy places a high degree of stress on the various tissues, ligaments and muscles of the pelvic floor which can also tear during childbirth thus resulting in this condition.
3. Hysterectomy which is surgery that involves the removal of the uterus that is a very important part of the support network complex in the pelvis can cause a drooping of the upper part of the vagina leading to a vault prolapse.
4. Other causes include ageing, chronic constipation, obesity and certain connective tissue disorders.

Symptoms and signs to look out for in POP
This will depend on the kind of prolapse that you are suffering from however; the most common symptom is the experience a dragging sensation or sensation of something that has come down in the vagina. Other symptoms may include pelvic discomfort or a lack of sensation during intercourse, difficulty having a bowel movement or bladder weakness leading to incontinence.

How is this condition diagnosed?
If you believe you are experiencing symptoms associated with POP, you should seek a consultation with a specialist in pelvic floor problems.

During the initial evaluation, the specialist will take a detailed medical history, looking for factors that may have contributed to this condition and perform a thorough pelvic examination.

Your doctor is likely to measure the position of your uterus to determine how severely it has dropped or "prolapsed". In addition, part of the exam may sometime be performed while you are standing to gauge the severity of the condition. The doctor may ask you to bear down like you were having bowel movement or cough. These actions make the pelvic injury more obvious.

Diagnostic tests, such as urodynamic studies to evaluate bladder function or special imaging studies to visualise the bladder or rectum may subsequently be arranged.

What can be done for POP?
Not all women with POP have symptoms that require treatment. The treatment that is best for you will depend on many things – your symptoms and their effect on your life, your age and your plans for pregnancy, and your expectations for treatment.

Intensive and regular **pelvic floor exercises** help by both strengthening and relaxing the

"Pelvic reconstructive surgery can be performed through the vagina or abdominally (via a traditional incision or through laparoscopy/ 'key-hole surgery')"

pelvic floor muscles so they become firm and supportive, but not overactive. Many women will have a major improvement in or recovery from symptoms of prolapse by learning effective pelvic floor exercises, thus avoiding or delaying the need for surgery. It is important to learn to do the exercises in the right way, and to check from time to time that you are still doing them correctly. Hence it is recommended that women see a specialist pelvic floor physiotherapist to take them through these exercises. Women who require surgery usually have a much better result if they work with an experienced physiotherapist before and after their procedure.

In addition to exercises women may find **medication** such as oestrogen replacement or **basic health and lifestyle changes** such as dietary change or treating constipation and managing to lose weight may bring relief to their symptoms.

A **vaginal pessary** to support the prolapse is a good short or long-term solution. Short-term pessary use is appropriate for women to make them more comfortable if a planned surgery needs to be delayed. Some women with slight prolapse are only symptomatic at certain times, such as when they are playing golf or tennis, and find a pessary useful on an as-needed basis. There are multiple types of pessaries, and finding the right pessary in the right size is the key to success. Some women have had a negative pessary experience and feel as a result that they are not a good candidate, when in fact the pessary was the wrong type or did not fit properly.

These conservative treatment options are usually offered to most patients before considering surgery. However if these fail and the symptoms are compromising the quality of life significantly then surgery to repair the prolapse is an option.

Pelvic reconstructive surgery can be performed through the vagina or abdominally (via a traditional incision or through laparoscopy/ 'key-hole surgery'). During the procedure, the surgeon will reposition the prolapsed organ(s) and secure the surrounding tissues and ligaments. The vaginal defect(s) which cause the bulge in vagina will also be repaired. Usually a repair of the perineum to support the opening of the vagina may be performed. Prior to undergoing surgery, patients should undergo a thorough evaluation to ensure a proper diagnosis. For example, some women may have stress urinary incontinence (leaking with coughing or sneezing) and may require a sling procedure performed at the same time to correct urinary incontinence, however in some circumstances this is best done as a two stage procedure which will be discussed with your doctor. Surgery for prolapse has three key issues which are:

1. failure of treatment of recurrence of symptoms
2. the chance of developing new troublesome symptoms such as worsening incontinence, pain due to scarring or pain with sex and change in bowel habit
3. complications of surgery including infection, bleeding, rarely injury to the surrounding organs

Therefore surgery to improve prolapse symptoms needs to considered ideally when all other options have failed and when the patient's quality of life is severely affected enough to merit accepting the above key issues.

Many women are embarrassed about seeking treatment for pelvic organ prolapse. Prolapse often causes women to feel embarrassed and needlessly self-conscious despite it being so common. The possible reason is that women rarely feel comfortable talking to their friends and family about such intimate matters. The good news is that women do not have to suffer in silence and live with the condition. Seek help early and women can be empowered to do something about pelvic organ prolapse, and they will have choices to suit their individual needs.

Please visit http://www.iuga.org/?patientinfo for more valuable patient information leaflets on prolapse and its treatment options.

Preetkiron Bhal *has been a Consultant Gynaecologist in Cardiff since 2003 with an interest in urinary incontinence, pelvic organ prolapse, general gynaecology and infertility. Mr Bhal is an expert in advanced vaginal and laparoscopic surgery. He offers a comprehensive service for managing urogynaecological problems including vaginal mesh related problems. Mr Bhal leads a multidisciplinary team in Cardiff striving to deliver the best available care for patients with bladder and pelvic floor conditions in South Wales. Mr. Bhal has continued with his passion for research and evidence based medicine and has presented work at numerous meetings both nationally and internationally.*

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REPROMEDA BIOLOGY PARK

Detecting Chromosomal Anomalies in Early Embryos through Preimplantation Genetic Screening (PGS)

By Kateřina Veselá

Reproduction genetics is continuously becoming one of the most important focus areas of assisted reproduction centres. Although it may not seem obvious, infertility, particularly infertility caused by advanced maternal age, is very closely linked to genetic factors. Numerical chromosomal anomalies, so called aneuploidies, arising in female oocytes, are one of the most serious causes of infertility. Many studies have confirmed that the number of aneuploidies occurring in oocytes increases significantly with advancing female age. These aneuploidies can be detected in early embryos through preimplantation genetic screening (PGS). In addition to this, PGS methods are currently not limited only to aneuploidy screening. Assisted reproduction centres are now able to provide help for clients not only with fertility problems, but also for couples with chromosomal translocations (often resulting in miscarriage or high-risk pregnancies), hereditary diseases or predisposition to cancer.

PGS, which is carried out in the course of the IVF treatment, allows us to transfer perspective embryos with a normal chromosomal set, i.e. euploid embryos, into the uterus. These embryos have a higher implantation potential, a lower abortion rate, and hopefully an overall higher chance of leading to the birth of a healthy offspring.

Incorrect chromosomal numbers in embryos are one of the most significant causes of embryo implantation failures and of unsuccessful IVF cycles in general. Most types of aneuploidies are not compatible with life, although in specific cases, chromosomal abnormalities, may lead to live births of affected foetus. The most common and well known conditions caused by chromosome aneuploidies include Down syndrome (extra chromosome 21), Patau syndrome (extra chromosome 13), or Edward syndrome (extra chromosome 18). However, the majority of these pregnancies end with foetal abortions (either spontaneous or induced).

PGS aims at improving pregnancy and live birth rates by embryo screening for chromosomal abnormalities. Screening is conducted in the shortest time and by the safest therapeutic means possible. Other advantages of PGS include:

- Reduction rate in miscarriages
- Decrease in the rate of pregnancy complications
- Treatment time and cost reduction, via decreasing the number of cycles necessary

- Multiple pregnancies reduction, due to one-embryo-only transfer policies
- Providing crucial diagnostic information, allowing the patient to decide whether to undergo another IVF cycle or consider gamete donation.

Without PGS, embryos for uterus transfer are selected solely on their visual quality, morphology, and growth dynamics. Regrettably, these criteria are not sufficient to exclude embryos with genetic abnormalities.

Due to preimplantation screening, we can inspect genetic qualities of selected embryos and consequently choose an embryo suitable for embryo transfer. This morphological and genetic selection ensures an increased embryo implantation potential and a decreased abortion rate. Therefore, couples with a poor chance of IVF success, can significantly improve their odds and their embryo implantation potential by genetic screening. These couples then have the same chance of embryo implantation as other couples, which is more than 40% for a single embryo transfer.

"The newest approach for aneuploidy screening is next-generation sequencing (NGS). This method not only allows us to detect all 24 chromosome abnormities, but also determines the percentage of cells carrying the detected aneuploidy"

Preimplantation genetic screening is strongly advisable for the following couples:

- advanced maternal age couples
- couples with repeated IVF failure and unsuccessful embryo transfers
- recurrent pregnancy losses and impaired child births (caused by chromosomal abnormalities)
- men with an abnormal sperm analysis (presence of pathological sperm forms) and low sperm concentrations
- couples that are carriers of chromosomal translocations and abnormalities
- use of TESE, MESA samples for fertilisation
- couples after a chemotherapy or actinotherapy for oncological diseases

Because preimplantation genetic screening increases the success of each IVF cycle, it is recommendable not only to couples with a genetic risk.

The newest approach for aneuploidy screening is next-generation sequencing (NGS). This method not only allows us to detect all 24 chromosome abnormities, but also determines the percentage of cells carrying the detected aneuploidy. Embryos can contain several cell lines with different chromosome complements. This phenomenon, when cells from one embryo carry a different chromosomal number, is called mosaicism. Mosaic embryo transfer, although sometimes resulting in healthy childbirths also carries with it many risks – such as a lower implantation rate and a higher abortion rate (in comparison to transfers of euploid embryos).

Mosaicism detection is therefore one of the main advantages of next-generation sequencing, in comparison to chip based comparative genomic hybridisation (aCGH),which is limited by its resolution.

Currently an obsolete method of aneuploidy detection is fluorescent in situ hybridisation (FISH), allowing detection of certain chromosomes only, making it nowadays unsuitable for PGS.

Preimplantation genetic diagnostics is, unlike genetic screening, a set of methods specifically targeting the transmission of a certain genetic risk or condition from one or both parents to their offspring. This may be, for example, a structural chromosomal abnormality, frequently a chromosomal translocation. Chromosomal translocations are detected in a manner similar to PGS, but with a higher resolution potential, allowing us not only to distinguish full chromosomal abnormalities, but also small chromosomal section alterations. Each couple prior to IVF treatment undergoes karyotyping to diagnose potential chromosomal abnormities or rearrangements e.g. translocations.

Another big group of disorders targeted by preimplantation genetic diagnosis are rare inherited disorders. Rare inherited disorders (also called monogenic diseases) are a very variable group of severe conditions, oncogenic predispositions and syndromes caused by genetic factors. Although these diseases vary significantly, they share the same origin: a single-gene mutation. It is possible to perform PGD for known mutations (either point mutations, repetitions, deletions or inversions), and therefore select unaffected embryos.

The most up-to-date method of PGD for rare inherited disorders is karyomapping, based on a whole genome detection of single-nucleotide polymorphisms. It is the whole genome coverage that allows us to detect various human single-gene mutations in embryos in the course of a normal IVF cycle. This represents a big advantage to the previously used PCR (polymerase chain reaction) based methods for single-gene mutation detection.

In view of the fact that only DNA of the treated couple and a single reference of known disease status (either from an offspring or from any other affected relative) is necessary, karyomapping significantly eases the stress, which the treated family is exposed to. In some cases, only DNA of the treated couple is sufficient for obtaining a clear result. By evaluating a single reference sample with DNA samples of the treated couple, we are able to mark the set of genetic information characteristic for the specific mutation (a haplotype linked with the mutation) and therefore exclude affected embryos from transfer. Hence, karyomapping represents an exquisite tool for termination of transmission of rare inherited disorders in the affected family.

In addition to rare inherited diseases, this method is also suitable for detection of some oncological predispositions, such as BRCA1 and BRCA2 gene mutations.

Karyomapping is also the only known tool, allowing us to detect balanced translocations in embryos. Balanced translocations are inherited from parent to offspring and their carriers often do not show any visible symptoms. Nevertheless, balanced translocations are a frequent cause of aneuploidies in embryos. Through karyomapping it is possible to distinguish between embryos carrying these types of translocations and between completely unaffected embryos.

Last, but not least, karyomapping also allows us to perform chromosomal screening for aneuploidies. We are now able to select embryos not only without inherited single-gene defects,

“Preimplantation genetic screening for aneuploidy is characteristic for all up-to-date PGD methods”

but also without aneuploidies; thus, we significantly increase the embryo implantation rate and decrease the abortion rate.

It comes as no surprise, that preimplantation genetic screening for aneuploidy is characteristic for all up-to-date PGD methods. Why focus only on a specific single-gene disorder and overlook all risks linked to aneuploidies, if we have the means to target both, the single gene disorders and aneuploidies, at the same time?

<u>Claim 1</u>: An increasing number of couples cannot be effectively treated for infertility, without the use of up-to-date genetic methods.
<u>Claim 2:</u> Karyomapping is suitable for any rare inherited disorder with a known causal mutation.
<u>Claim 3:</u> Only the PGS method is suitable for a full analysis of all chromosomes.

MUDr. Kateřina Veselá, Ph.D. was born on 21. 5. 1966. She successfully graduated from the Faculty of Medicine, Masaryk University Brno and has obtained a postgraduate certification in obstetrics and gynecology. She acquired her Ph.D. title in the field of medical biology and genetics. Currently she acts as a managing director in REPROMEDA, a center of assisted reproduction medicine and genetics. In 2000, the first successful cycles with preimplantation genetic diagnostics in Central Europe were carried out under her supervision. Her center of assisted reproduction currently performs approximately 500 preimplantation genetic diagnostic runs annually. She is now an internationally respected specialist in the field of reproductive medicine and genetics.

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Ectopic Pregnancy "Extra uterine pregnancy"

By Dr. S Michael Awad

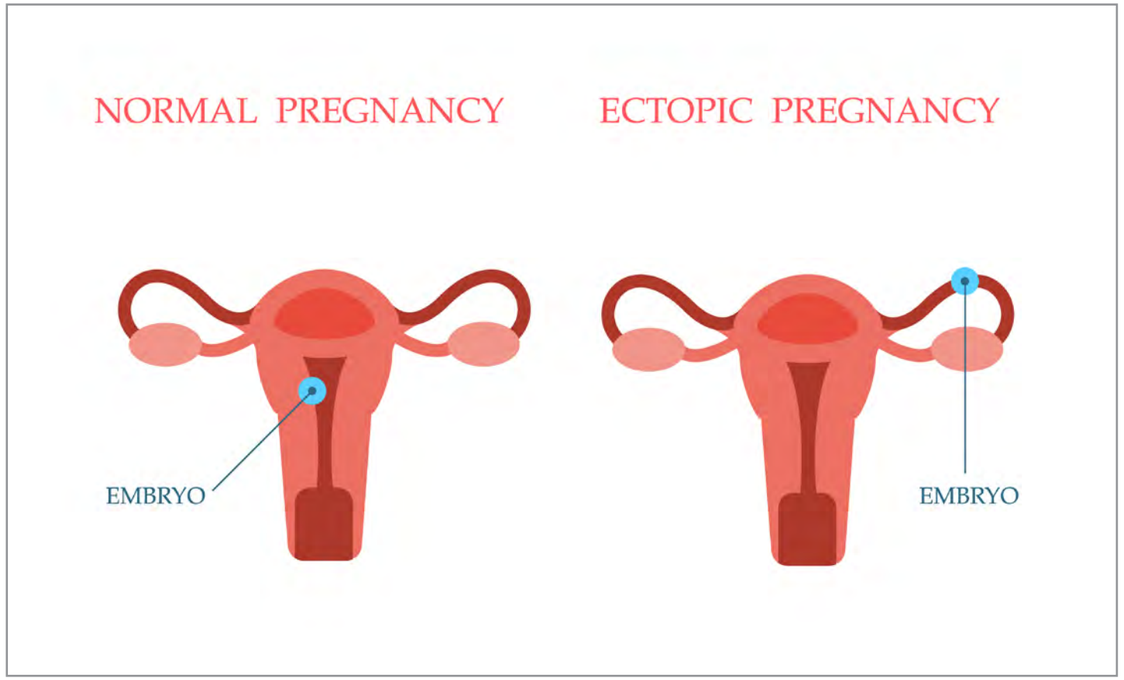
Ectopic pregnancy is a pregnancy that occurs, or implants outside the recognised endometrial cavity. The condition significantly contributes to maternal mortality all over the world, due to five very important factors:

1. Lack of early detection and diagnosis.
2. Lack of early intervention, especially if the patient doesn't have quick access to safe surgery/surgeon.
3. The speed of progression of the case from being haemodynamically stable into very critically unstable patient, that require professional, fast and adequate intervention to deal with the emergency, including intensive monitoring, central line access, continuous blood pressure, pulse arterial oxygen monitoring, blood transfusion, operating room available at very short notice and personnel that carry out emergency laparoscopy/laparotomy.
4. The early symptoms can pass undetected.
5. Lack of suspicion of diagnosis or differential diagnosis of the condition, which makes early detection difficult.

By definition, an ectopic pregnancy (EP) is pregnancy implanted outside the endometrial cavity. That can occur in any part of the Fallopian tube, on the surface of the ovary or inside the abdominal cavity. Fortunately, at just 6-16% of all pregnancies, it is not a very common condition. However it is becoming more common than it was 20-30 years ago, and if it is not treated early it can result in maternal death.

Approximately 95% of EP pregnancies occur in the Fallopian tube, 2.5% occur in the uterine cornua and 2.5% occur on the ovary or inside the abdominal cavity. Naturally, symptoms can vary based on the site of the EP. For instance, in cases of corneal EP, abdominal pain and rupture of the cornua occur much earlier than if the EP occurs in the ampullary portion of the tube, where pain is a late symptom and spontaneous abortion from the end of the tube can occur, resolving the condition.

There is a trend pattern emerging which links the rise of sexually transmitted diseases or infections (STD or STI) with EP pregnancies. In geographic areas where STD/STI is on the rise, EP pregnancies are also increasing. Likewise, EP pregnancies are lower in areas where STD/STI is low. More surgeries carried out on the Fallopian tubes will lead to more EP occurrence. That includes tubal ligation, which may not achieve complete occlusion to the tubal lumen or cavity. Tubal reconstruction, adhesiolysis by any format, cuff salpingostomy and end-to-end reanastomosis can all contribute to increased incidence of EP.



As egg fertilisation and the formation of early embryo and zygote occur in the outer third of the Fallopian tube, any scars, twist, distortion or disruption to the ciliary action of the tubal endothelium, can be the etiology of EP, as the zygote can't proceed to its destination inside the endometrial cavity.

Also, an increase in tubal disease will lead to an increase in EP. Tubal disease is caused mainly by ascending infection, including STD/STI as mentioned before. Tubal disease may be microscopic and can't be detected on laparoscopy, saline hysterograph or dye hysterosalpingogram, as the pathology is at the level of endothelial function. Macroscopic pathology can also occur as tubal obstruction and variety of hydrosalpinx affecting any part of the tube, usually the distal and mid portion of the tube.

One more factor in the etiology of EP. That is the increase in ART (Assisted Reproductive Technologies). As pregnancies due to ART is on the rise, so EP is. Most of these cases has microscopic and undetected tubal factor, which arrest the migration of the early embryo and stops it inside the tube.

With such potentially lethal condition, how can we diagnose it early? The holly triad is:

1. positive pregnancy test
2. pain, usually lower quadrant or pelvic
3. irregular and erratic vaginal bleeding. Our suspicions should be sharply increased for ectopic if the following triggers;

"If you have enough clinical suspicious, then you should start building up your diagnosis. Clinical examination is not usually helpful, and you have to be careful with pelvic exams, as it may trigger severe pain and induce tubal rupture and significant pelvic bleeding"

- Previous STD, especially Chlamydia
- Previous EP whether treated medically or surgically.
- Previous tubal surgery, reconstructive or reanastomosis.
- History of ART, IUI, insemination, ovulation induction.

If you have enough clinical suspicious, then you should start building up your diagnosis. Clinical examination is not usually helpful, and you have to be careful with pelvic exams, as it may trigger severe pain and induce tubal rupture and significant pelvic bleeding. In fact, if you are sure you are dealing with EP; pelvic internal exam should be avoided and prohibited.

That leaves us with only two critical examinations; quantitative serum B-HCG (Se. B-HCG) level and endovaginal ultrasound examination with or without Doppler exam.

With quantitative serum B-HCG level, it has been serial measurements and the result should be available within 24 hours if not less and shouldn't be more. In a healthy pregnancy, even if there is no diagnosis on ultrasound or the ultrasound has diagnosed what is known as "pregnancy of unknown location"; the serial measurement of Se. B-HCG should confirm steady and continuous rising, which doubles up in value every 48 to 72 hours. Therefore, we ask to repeat the measurement of quantitative serum B-HCG level every two to three days, till ultrasound can give us clear answer of where the pregnancy is located. If the quantitative serum B-HCG levels are static, not rising or doubling every 2-3 days or dropping, the diagnosis of EP is highly suspected. It is not pathognomonic however, as this can also happen with early pregnancy failure, blighted ovum or early foetal demise. The second critical test, i.e. ultrasound can differentiate between all these.

Ultrasound examination is a corner stone in our diagnosis of EP. With the advances of ultrasound high resolution and HD, liberal use of endovaginal scanning and Doppler examination, major improvement happened in the diagnosis of EP in the last 15 to 20 years. Careful examination of any adnexal mass should be carried out, especially if it increases in size on subsequent ultrasound examination, with evidence of vascularity on Doppler assessment. Sometimes gestational sac can be detected in adnexa with or without fetal pole and fetal heart. If this is seen, you have a real emergency on your hands.

Now, you have patient with abdominal quadrant pain, steady or declining quantitative serum B-HCG level, mass in adnexa with increased Doppler blood flow around it. The diagnosis is adnexal EP. A plan of management should be laid out and discussed with the patient, partner or family if available, based upon a number of key determinations, namely: the other symptoms of pain severity, how is the BP, pulse rate, desire for future fertility, cardiovascular stability of patient. We should take into account other factors including known pelvic conditions like adhesions, endometriosis, previous tubal surgery, history of previous EP or tubal ligation. Diagnostic laparoscopy may be considered to confirm the diagnosis, plus or minus other laparoscopic intervention, like Methotrexate injection into the EP, adhesiolysis, removal of the ectopic tissue and conservation of the tube or removal of the tube with the ectopic pregnancy as one block. Laparoscopy for diagnosis alone is not common, especially with the availability of accurate quantitative serum B-HCG assay and sensitive ultrasound. The use of diagnostic laparoscopy is on the decline. It remains however a cornerstone in the surgical treatment.

Once the diagnosis of EP has been confirmed and you are comfortable with it, the next stage is to establish the method in which it will be managed, depending upon the aforementioned factors. It will lie between:

- **Medical intervention**; that will include the use of Methotrexate (MTX) with education to patient, arranging follow up and managing her pain till the condition is resolved.
- **Surgical intervention**; that is usually laparoscopic intervention aiming at: i.) removal of the ectopic tissue from the tube, ii.) stopping the tubal bleeding, iii.) ensuring the opposite tube is healthy and normal looking, and iv.) inspecting the rest of the pelvis to exclude other diseases. In rare occasions, especially when the patient is hemodynamically unstable, emergency STAT laparotomy can be employed, accompanied simultaneously with adequate and competent resuscitation especially blood replacement to compensate for significant blood loss that can occur inside the peritoneal cavity.

What are the choices of surgical treatment of EP? If no further fertility or children is required, then salpingectomy will be in order. It is easy to do laparoscopic and usually no need for post op follow up with quantitative serum B-HCG measurement.

However, in the majority of cases, further fertility is required. In this case, there are three surgeries can be applied:

Laparoscopic injection of MTX into the EP under direct vision. If a needle is inserted into the tubal swelling, blood can be aspirated first, or

"In extreme cases, one can do segmental resection of the tube where the EP is followed by end-to-end anastomosis of the tube, all in one session"

some saline flush with 5 ml of saline can be injected first, and then aspirated before 1 ml of 50 mg MTX is injected into the EP. Follow up with serial measurement of quantitative serum B-HCG level must be done every 2-3 days to make sure of complete resolution of the EP.

Laparoscopic linear salpingostomy, along the anti-mesenteric border of the tube, where most of the swelling is, followed by aspiration of blood and clots trapped inside the tube, then removal of the ectopic and trophoplastic tissue from the wall of the tube with atraumatic laparoscopic grasper, flushing the inside of the tube and stabilising all bleeding points. It is advised to inject diluted vasoconstrictives into the mesosalpinx just underneath the EP before you start slicing.

In extreme cases, one can do segmental resection of the tube where the EP is followed by end-to-end anastomosis of the tube, all in one session. Fertility can be maintained in such a case, especially when the other tube is compromised.

On rare occasions, conservative management and observation may be advised. That is usually limited to conditions when tubal spontaneous abortion has occurred, and the clinician believe that the EP has been expelled from the end of the tube, into the peritoneal and pelvic cavity. It is exceedingly rare that the EP that expelled from the tube can attach itself somewhere in the pelvic or peritoneal cavity and revive again. The patient should be monitored with frequent office or outpatient visits, repeated ultrasound and most important measurement of quantitative serum B-HCG level till we obtain at least one if not two reading of less than 4-5, indicating complete disappearance of the B-HCG from the circulation.

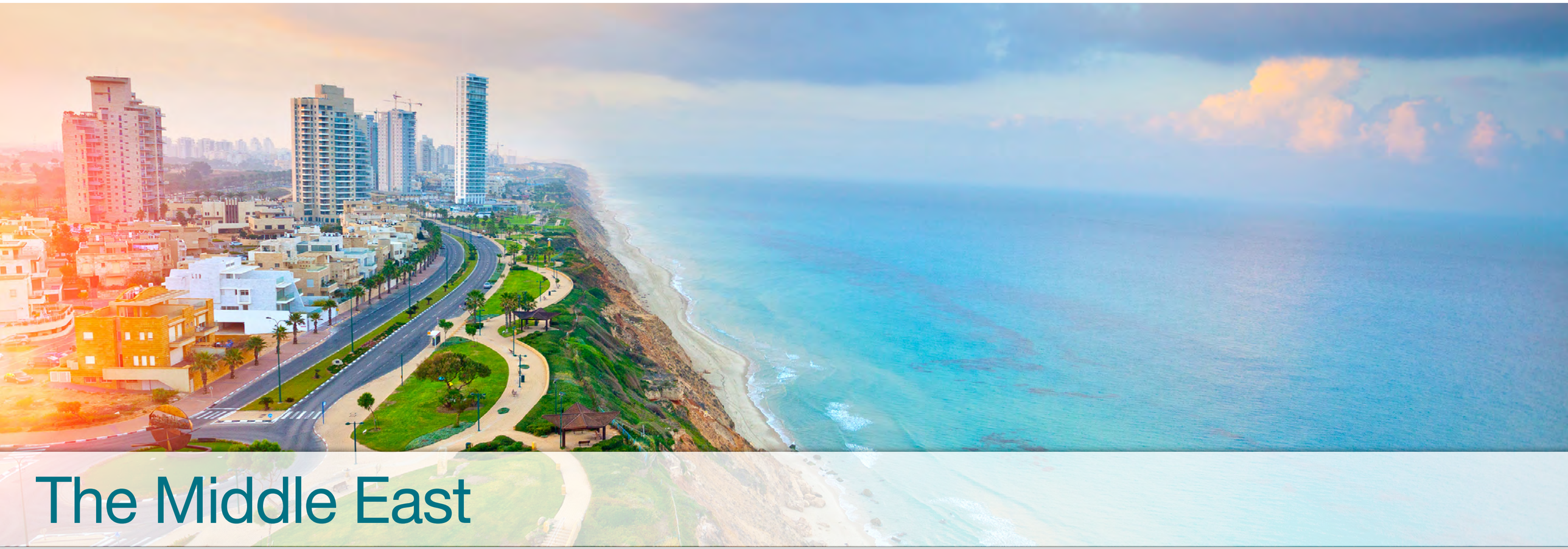
Now, I need to expand on the use of cytotoxic medical treatment of EP. Methotrexate is the drug of choice for EP. The dose chosen for this drug is 50 mg per square meter of body surface area. I clinical use, the dose usually vary from 75 to 190 mg, given as single dose IM. When the dose was chosen in 1980s, it was chosen on empirical basis. I'm not quite sure why the 50 mg was chosen. I review the published medical literature, and couldn't find a single trial where 50 mg MTX was compared with 40, 60, 80 or 100 mg per square metre. It was also quoted that the success rate of 50 mg is 80-90% success rate based on few number patients' trial. I have to question few things here;

- I doubt the success rate is as high as they claim it to be. In my practice, I observed a success rate of only 70-75%. That means almost a failure rate of medical treatment of 25-30%. In my personal opinion that failure rate is too high.
- The selected dose of 50 mg, never took account of patient's body habitué, the level of serum B-HCG (whether it is 50 or 5000), the size of adnexal mass as measured on ultrasound (whether it is 1 or 5cm) and whether there is gestational sac visible in the adnexa, with or without fetal pole and fetal heart beat. These are very serious shortcoming that was not taken into account when deciding on 50 mg dose. It is probable that they wanted to be on the safe and low dosage side. The criticism here is, they never tried higher dose, especially in the conditions that logically needs higher dose; e.g. higher BMI, high serum level of B-HCG at initiation of treatment and development of gestational sac in adnexa.
- The safety range of MTX is huge, and it has been used up to a maximum dose of 20,000 mg a day. If the safety margin of the drug is that high, why do we use minuscule dosage (75-190 mg) as we do today. It is not make sense.
- Finally, lack of adequate clinical trials with higher or other dosage than 50 mg per square metre, is very surprising to me, that the whole profession accepted the 50 mg dosage without any challenges.

I would like to suggest that we should give double the recommended dose that everyone uses. In other words, we should be giving 100 mg per square meter of body surface, in the following conditions;

- If the patient in moderate degree of pain, and is keen to resolve her EP faster.
- If the serum level of B-HCG is over 1,000.
- If the adnexal mass is more than 1cm in maximum diameter, on endovaginal ultrasound exam.
- If the patient BMI is higher than 30.
- I hope gradually, this dose of 100 mg/sq metre should be given to everyone who wants to avoid tubal rupture, emergency laparoscopy or laparotomy for significant intra-abdominal bleeding.

With early detection, high degree of suspicion of EP and adequate use of dosage of MTX, we can avoid emergency surgery and the life threatening condition of EP.



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עמותת חן לפריון וחיים
"CHEN" - Patients Fertility Association

Egg donation law - The Israeli case

By Ofra Balaban-Kasztelanski

In Israel, there is a strong and valid legislation with regulations regarding egg donation. The story started in 1987 when the Ministry of Health enacted a law to allow egg donation in Israel with the in-vitro fertilisation (IVF). The latest chapter closed in 2011 when the new law passed the 3 votes in the Knessett.

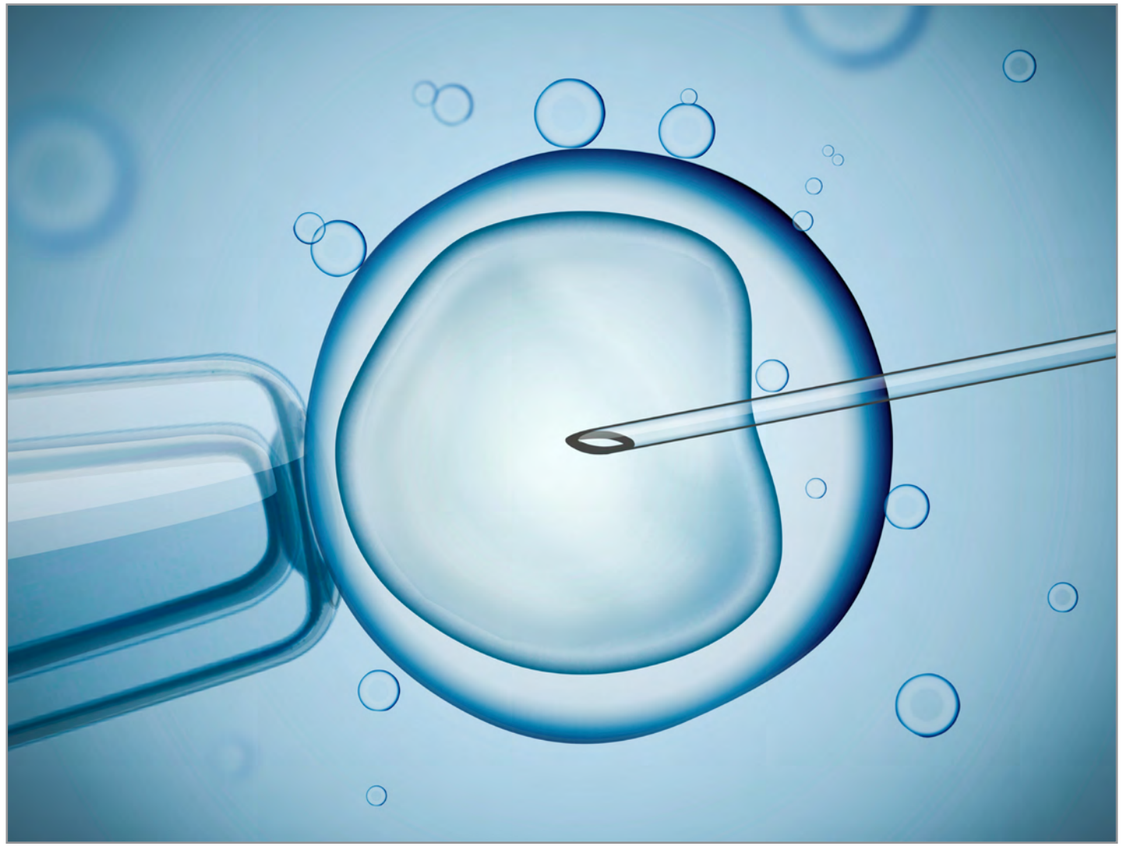
The law of 1987 and regulations regarding donation were very clear: If a woman needed to have an egg donation she may get an egg donation from Israeli woman that is already an IVF patient. It was not allowed to have egg donation from healthy women that are not patients. The logic surrounding this decision and the level of risks those days were too high so only a patient could donate to another patient. As scientific and technological advances were made the law became dated. In 1998, Israel started the long procedure of changing the law so that a healthy woman can donate eggs. It took us 13 years and lot of deliberation in the Israeli parliament – the Knessett – until the legislation was finally completed. The following extract is a short version of the law that contains 55 clauses guarding the donor, the recipient and the newborn:

The new legislation allowed a healthy woman under the age of 35, to donate her eggs to a patient with the conditions of anonymity. Israel is a small country and it is important to keep anonymity and sealed details. All details of donor and recipient are sealed. The only body that can give any information is Family court – young couple can apply to the court only with identity numbers and the court will check if there is any genetic relations between them as first degree family or not. All other details are sealed and cannot be revealed at all.

Women can have an egg donation until one day before their 54th birthday, in 7 out of 28 public clinics in Israel from an Israeli donor. The state covered the cost of egg donation but not the price of the sperm. The patient has to pay 10,000 SHEKELS as part of the payment to the donor that is being done via the clinic. The Ministry of Health matches the same amount. All of the procedure must take place in the clinic.

Cross-border egg donation is allowed and the state participates in the costs – about 30% is covered. In this case there is no regulation regarding the sperm or the egg origin.

Our next legislation is embryos donation in Israel. With the cooperation of the Ministry of Health we gathered the government and the Knessett to work together for the preparation of the law. This is one of the strong abilities of NGO in Israel – changing the law for the benefit of our patients.



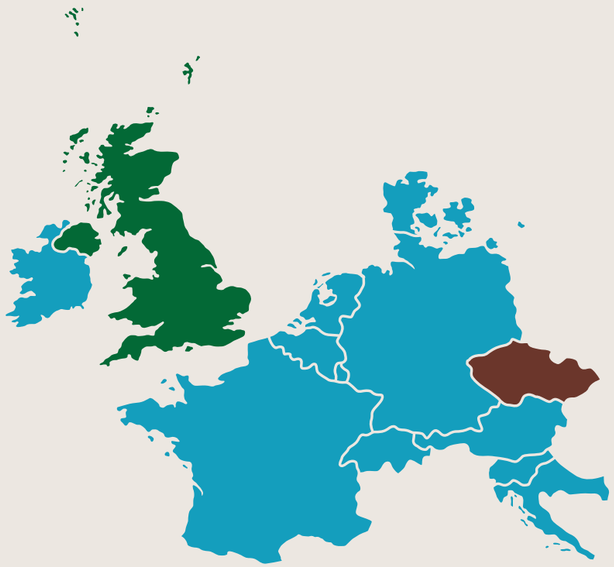
Since 1998 – I am the founder and the chair of CHEN – Patient Fertility Association, fully volunteered, supports infertile couples and educated youth.

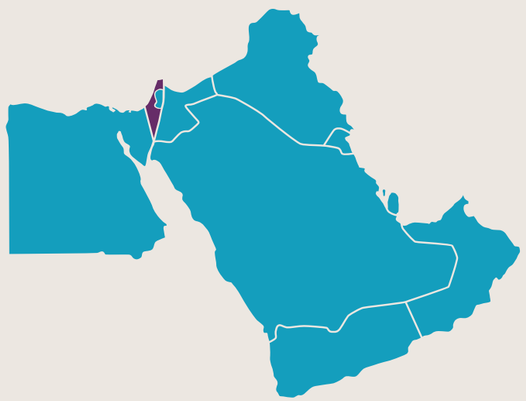
Representing Israel in the international umbrella organizations:
Fertility EUROPE – The European roof organization for patient fertility associations. Since 2016 – Member of the board.
ICSI (International Consumer Support for Infertility) and AFAM (USA)– (member of the board). IAPO – the global organization of patients.
EPHA – The European public health alliance.
EPF – European patient forum
EPHA –The European public health alliance. I am an active member.

In Israel: women council in Holon and volunteers council and the women council.

2006 –Volunteer of the year.

Expert Directory





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