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Changing Attitudes in Obstetrics and Gynecology – How Evidence Based Medicine is Changing Our Practice?

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1. Introduction

Evidence-based medicine (EBM) is the process of systematically reviewing, appraising and using clinical research findings to aid the delivery of optimum clinical care to patients (Rosenberg and Donald, 1995). It is considered a new trend in both teaching medicine and supporting the clinical decisive process, answering the clinical questions. The basis of the evidence-based medicine comprises of analysing and interpreting current and reliable medical publications concerning certain subject (Laudański and Pierzyński., 2000).

Evidence-based practice is "a process of care that takes the patient and his or her preferences and actions, the clinical setting including the resources available, and current and applicable scientific evidence, and knits the three together using the clinical expertise and training of the health-care providers." (Haynes *et al*., 2002).

Thus, EBP as illustrated in Figure (1) is the integration of *clinical expertise*, *patient values*, and the *best research evidence* into the decision making process for patient care. Clinical expertise refers to the clinician's cumulated experience, education and clinical skills. The patient brings to the encounter his or her own personal and unique concerns, expectations, and values. The best evidence is usually found in clinically relevant research that has been conducted using sound methodology (Sackett *et al*., 2000).

Despite its ancient origins, evidence based medicine remains a relatively young discipline whose positive impacts are just beginning to be validated, and it will continue to evolve (Bennett *et al*., 1987; Shin *et al*., 1993).

The aim of this chapter is to explore different aspects of evidence based medicine including background on its development, motives towards changing our attitudes in practice and how can evidence be extracted. The chapter will also highlight the major role of evidence based medicine in changing attitudes towards evidence based practice which ensures safety and efficiency of the health service provided, in the field of obstetrics and gynecology; a domain that has greatly participated in the establishment of evidence based medicine and evidence based practice. Many examples on how evidence based medicine has changed attitudes in practice will be displayed to demonstrate and emphasize this role.

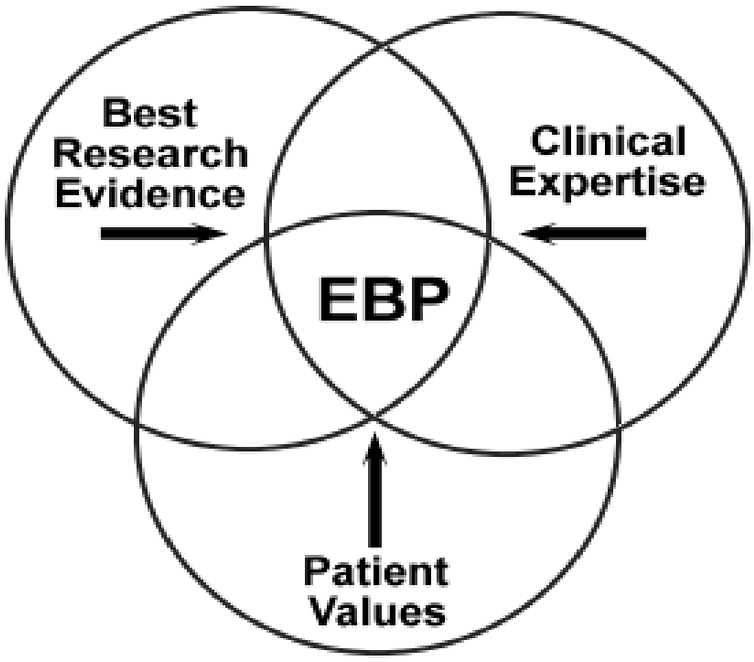

Fig. 1. Evidence Based Practice (EBP)

2. Why changing attitudes in practice

Although clinical research is consistently producing new findings that may contribute to effective and efficient patient care, the findings of such research will not change population outcomes unless health services and health care professionals adopt them in practice (Grimshaw *et al*., 2001).

However, the enormous volume of information that is published in an ever-increasing number of available medical journals constitute a major obstacle and a real challenge to obtaining reliable evidence for clinical practice from research. Over half a million papers on gynecology, infertility, pregnancy and obstetrics are published each year. To sift through these MEDLINE records, let alone the full papers that may be relevant, to identify those which should form the basis of clinical practice is an overwhelming and nearly impossible task. How, then, can busy clinicians have easy access to, and identify, the most appropriate information on which to base their clinical decisions? (Dodd and Crowther, 2006).

The contribution of evidence-based medicine to improved patient outcomes in general practice is incontestable. Evidence based practice promotes practices that have better outcomes and are scientifically proven to be effective. It aims to eliminate unsound or risky practices, thus improving quality of care, providing best service to the patient and promoting patient safety.

Actually, evidence based practice is one step toward making sure that each patient gets the best service possible. Furthermore, it helps physicians to keep knowledge up to date and supplements clinical judgment; very vital benefit especially in the light of the rapidly growing literature and medical advances.

3. Evidence based and experience oriented practice

Clinical medicine is currently in transition from experience-oriented practice to an evidence-based one which requires the best available evidence that answers our clinical questions for better safety and efficacy. However, there is a balance, and even tension, between evidence and clinical expertise:

"Without clinical expertise, practice risks becoming tyrannized by external evidence, for even excellent external evidence may be inapplicable to or inappropriate for an individual patient. Without current best external evidence, practice risks becoming rapidly out of date, to the detriment of patients." Good doctors use both individual clinical expertise and the best available external evidence, and neither alone is enough (Sackett et al., 1996).

Evidence based medicine helps clinicians to integrate the best external clinical evidence from systematic research with individual clinical expertise to make effective decisions about patient treatment and care.

Best available external clinical evidence means clinically relevant research, often from the basic sciences of medicine, but especially from patient centred clinical research into the accuracy and precision of diagnostic tests, the power of prognostic markers, and the efficacy and safety of therapeutic, rehabilitative, and preventive regimens.

External clinical evidence can inform, but can never replace, individual clinical expertise, and it is this expertise that decides whether the external evidence applies to the individual patient at all and, if so, how it should be integrated into a clinical decision (Sackett *et al*., 1996).

4. How can evidence be extracted?

The best evidence is usually found in clinically relevant research that has been conducted using sound methodology (Sackett *et al*., 2000). EBM is not restricted to randomized trials and meta-analyses. Actually, it involves tracking down the best external evidence with which to answer our clinical questions.

Thus, to find out about the accuracy of a *diagnostic test*, we need to find proper cross-sectional studies of patients clinically suspected of harboring the relevant disorder, not a randomized trial while for a question about *prognosis*, we need proper follow-up studies (i.e. prospective cohort studies) of patients assembled at a uniform, early point in the clinical course of their disease. And, sometimes, the evidence we need will come from the basic sciences, such as genetics or immunology.

It is when asking questions about *therapy* that we should try to avoid the non-experimental approaches, because these routinely lead to false-positive conclusions about efficacy. Because the randomized trial, and especially the systematic review of several randomized trials, is so much more likely to inform us and so much less likely to mislead us, it has become the "**gold standard**" for judging whether a treatment does more good than harm (Sackett et al., 1996).

5. Development of evidence based practice in obstetrics

Although the term 'evidence-based medicine' was first used by Gordon Guyatt of McMaster University, Canada, in 1990, (Guyatt and Rennie, 2002) the development of evidence-based

practice in obstetrics began in the early 1970s. Archie Cochrane, in his now well-known writings (Cochrane, 1972), awarded the 'wooden spoon' to obstetricians for having made the poorest use of randomized controlled trials, and having widely incorporated changes into clinical practice without appropriate evaluation(Cochrane, 1972).

Such observation inspired Iain Chalmers in 1974 to start the enormous task of collecting all randomized controlled trials related to the field of perinatal medicine. More than 3000 trials conducted between 1940 and 1984 were identified. This collection was first published in 1985 as the Oxford Database of Perinatal Trials (ODPT) (Chlamers *et al*., 1986). In 1989, the first comprehensive synthesis of evidence for pregnancy care, entitled "Effective Care in Pregnancy and Childbirth" (ECPC), was published; it included systematic reviews of the identified randomized trials (Enkin *et al.,* 1989).

This two-volume book was condensed into the paperback "A Guide to Effective Care in Pregnancy and Childbirth (GECPC)" summarizing the available evidence on the effects of pregnancy care, and categorizing care practices into those with evidence of known benefit, those of uncertain benefit, and those of known harm (Enkin *et al*., 1989). All of these early pregnancy and childbirth initiatives were important forerunners to the Cochrane Collaboration (The Cochrane Library, 2005).

6. Examples for how evidence based medicine changed practices in obstetrics and gynecology

We will be displaying in the coming section many practical examples elaborating the great noticeable role of evidence based medicine in shifting the practices in obstetrics and gynecology towards better safety and higher efficacy and in eliminating risky unsafe practices. Evidence based medicine has changed attitudes towards interventions, therapeutics and diagnostics.

6.1 Changing attitudes towards interventions (evidence based interventions)

What matters in health care is identifying and using interventions that have been shown by strong research evidence to achieve the best outcomes within available resources for everyone (Fletcher and Lancet, 1999). Examples for such interventions will be discussed.

6.1.1 The term breech trial

Among most issues in the field of obstetrics that have been very controversial is the breech delivery. Approximately 4% of all infants are in breech presentation. Delivery in this position is more difficult, with increased risk of complications to the fetus such as umbilical cord prolapse, hypoxia, and fetal injury.

Despite increased risks, breech deliveries are usually accomplished without complications and without the need for 'expert assistance' from an experienced, trained clinician or midwife. However, in the event that expert assistance is needed but not obtained, permanent damage can occur during breech births because of the lack of appropriate and well-timed actions by the birth attendant.

Historically, vaginal breech deliveries were considered the norm until 1959, when routine cesarean delivery was shown to reduce perinatal mortality and morbidity (Wright, 1959).

While there was a general belief that planned cesarean delivery was better than planned vaginal delivery for breech deliveries, evidence was inconclusive because most studies were observational, two small RCTs showed no difference, and evidence suggested that improved neonatal outcomes might occur at the expense of poorer maternal outcomes.

The Term Breech trial, a multi-center trial across 121 centers in 26 countries randomizing 2088 women to 'planned cesarean delivery' or 'planned vaginal' deliveries (1997 – 2000). The trial found during interim analyses that cesarean delivery was associated with a reduced risk of perinatal morbidity and mortality. The term breech trial had an immediate **dramatic impact** on the management of term breech deliveries with policies changed in accordance with the trials findings. Rapid change in clinical practice occurred in many locations, although not universally, as some desired more evidence and others were reticent to accept the trials results as conclusive (Hannah *et al*., 2000).

Several comparison studies showed alteration of clinical practice via examining rates of vaginal breech delivery versus cesarean delivery in various countries (e.g., New Zealand, Australia) (Kaushik and Gudgeon, 2003).

6.1.2 Examples of other obstetrical interventions

There was widespread variation in clinical practice in areas such as the role of external cephalic version (ECV) for breech presentation (effective in reducing the need for caesarean delivery), the use of prophylactic antibiotics at caesarean delivery (effective in reducing maternal puerperal sepsis), the use of antenatal corticosteroids for fetal lung maturation (effective in reducing the risk of neonatal respiratory disease and mortality in infants born preterm), the use of vacuum-assisted vaginal births (effective in reducing maternal vaginal and perineal trauma), and selective versus routine use of episiotomy (effective in reducing maternal perineal trauma).

The systematic reviews first published in Effective Care in Pregnancy and Childbirth (ECPC) and The Oxford Database of Perinatal Trials (ODPT), and by the Cochrane Collaboration Pregnancy and Childbirth review group, summarized the best available evidence at the time, indicating benefit for all of these interventions. For some of these interventions, clinical practice has indeed changed.

Prenatal corticosteroids are now widely prescribed for women at risk of preterm birth, with 82% of mothers of infants born at less than 34 weeks' gestation admitted to the neonatal intensive care unit in Australia, having been administered corticosteroids prior to birth (Donoghue *et al*., 2002). The uptake of ECV for breech presentation at term has been less successful, with only 67% of obstetricians surveyed in Australia and New Zealand offering ECV (Phipps *et al*., 2003).

6.1.3 The obstetrical outcomes after conservative treatment of intraepithelial neoplasia or early invasive lesions

With the establishment of effective screening programmes for cancer cervix, women are more commonly diagnosed early with preinvasive lesions and microinvasive cervical cancers which make younger women with such lesions candidate for conservative treatment for the sake of preservation of the potential for childbearing.

However, proper counseling of those young women on the effect of such conservative treatment on the obstetrical outcome has been problematic and inadequate till the emergence of an important **meta-analysis** performed by Kyrgiou *et al* in 2006 in which the authors have investigated the obstetric outcomes in women who underwent excisional procedures in the cervix (Kyrgiou *et al*., 2006).

In this meta-anlaysis, a total of 27 studies were included. The authors exhibited that cold knife cervical conisation was significantly associated with preterm delivery, low birth weight and cesarean delivery; similarly Large Loop Excision of the Transformation Zone (LLETZ) was associated with preterm delivery, low birth weight and premature rupture of the membranes. Similar but marginally non-significant adverse effects were recorded for laser conisation. But the investigators did not detect significantly increased risks for obstetric outcomes after laser ablation.

It was concluded that all the excisional procedures used to treat cervical intraepithelial neoplasia present similar pregnancy-related morbidity without apparent neonatal morbidity. This study changed the future attitude of gynecologists towards women with abnormal cervical lesions and alerted the physicians to be more cautious for future treatment options. This study also provided clinicians with evidence base to counsel women appropriately (Kyrgiou *et al*., 2006).

6.1.4 Preimplantation genetic screening for aneuploidies in IVF/ICSI

Despite the great advances that have taken place in the field of in vitro fertilization (IVF) since its introduction in 1978 with the achievement of considerable success rates in almost all causes of infertility, still many women fail to become pregnant in spite of repeated transfers of apparently morphologically normal embryos.

Among the highly accused causes for this repeated failure is the inherent abnormal chromosomal make-up of the embryos (i.e. embryonic aneuploidy) (Wilton, 2002). Other causes responsible for the pregnancy failure are the poor endometrial receptivity and the inefficiency of the embryo transfer techniques (Mansour and Aboulghar, 2002).

Many of the chromosome abnormalities observed in human embryos will cause the embryos to die early in development, sometimes even before implantation, or before term pregnancy can be reached.

Patient populations with certain characteristics (e.g. advanced maternal age, recurrent implantation failure , repeated miscarriages, patients undergoing testicular sperm extraction (TESE) and intracytoplasmic sperm injection (ICSI) have been considered at higher risk of producing aneuploid embryos (Kahraman *et al*., 2004; Munne *et al*., 2004; Gianaroli *et al*., 2005) which would die around the time of implantation and therefore result in no established pregnancy (Munne *et al*., 2003; Caglar *et al*., 2005).

In recent years, these observations of significant incidences of aneuploidy in early human embryos has led to the expansion of preimplantation genetic diagnosis techniques for aneuploidies (PGD-AS) to patients who are considered to have a poor prognosis of reaching a full-term pregnancy (Sermon *et al*., 2005).

Embryo morphology alone cannot be used to predict euploidy since many good quality embryos have been found to be aneuploid (Delhanty *et al.,* 1997; Harper *et al*., 1995; Magli *et al.,* 2001), thus genetic diagnosis is required to detect aneuploid embryos.

Two main techniques namely; fluorescent in situ hybridization (FISH) for multiple chromosomes and polymerase chain reaction (PCR), are used to document a high frequency of chromosomal errors and aneuploidy in human preimplantation embryos. These techniques enable the selection of chromosomally normal embryos that are more likely to implant.

PGD-AS is commonly also known as preimplantation genetic screening (PGS), with both terms used interchangeably. PGS needs to be differentiated from preimplantation genetic diagnosis (PGD). While the technology used in both techniques is almost identical, PGS and PGD differ mainly in their indications. PGD aims to prevent the birth of affected children in couples with a high risk of transmitting specific genetic disorders, whether numerical or structural in nature. PGS, on the other hand, aims to improve pregnancy rates in infertile couples undergoing IVF/ICSI treatment, and who do not have any chromosomal aberrations.

PGS allows the detection of aneuploidy before the step of embryo transfer. Aneuploid embryos could be screened out and only euploid ones transferred, thus theoretically increasing the chance of pregnancy and reducing the chance of miscarriage.

A recent systematic review and meta-analysis by **Abou-Setta *et al.,*** in 2011 aimed to evaluate whether PGS can improve the clinical outcomes of IVF/ICSI compared with no intervention. There was no significant difference in live birth rates following PGS compared with no PGS (R.R = 0.79, 95% CI: 0.54 to 1.15; p = 0.22; I^2 = 65.74%, 95% uCI: 10.51% to 86.89%) (Figure 2). As well, there was no significant difference in clinical pregnancy rate following PGS compared with no PGS (R.R = 0.89, 95% CI: 0.67 to 1.17; p = 0.40; I^2 = 62.00%, 95% uCI: 1.70% to 76.66%) (Figure 3).

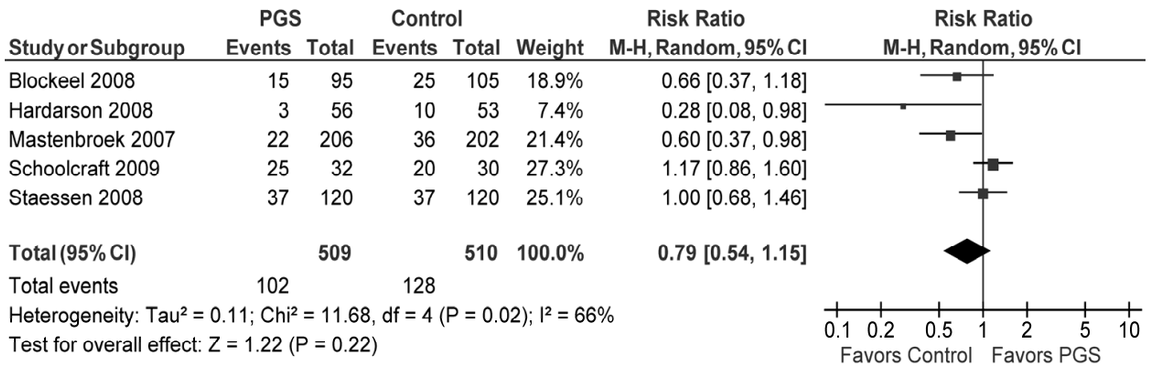

Fig. 2. Forest plot of comparison: PGS vs Control Live birth rate

The results of this systematic review showed that until today, there was no enough evidence in the literature to give a conclusive decision on the value of PGS for patients undergoing IVF/ICSI. Currently with the evidence at hand, PGS seems to have no impact on improving live birth rate (Figure 2) and the clinical pregnancy rate (Figure 3) in patients undergoing IVF/ICSI. In fact, many of the trials were not completed and were stopped early because of the ineffectiveness of the intervention **(Abou-setta *et al*., 2011).**

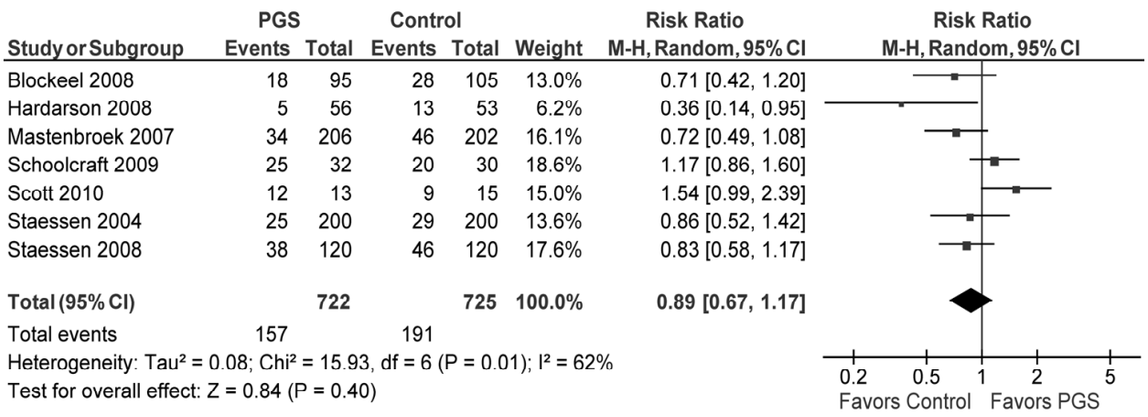

Fig. 3. Forest plot of comparison: PGS Vs Control Clinical pregnancy rate

6.2 Changing attitudes towards therapeutics (evidence based therapeutics)

The advances in therapeutics are tremendous with many novel drugs and therapies manufactured and developed every day with the emergence of new strategies and mechanisms of actions making the selection of the best effective therapy a difficult and challenging task. Evaluation of the superiority of a particular therapy based on a single trial is inadequate and deficient. Hence, for evaluation to be better and adequate, it should be served by a comprehensive and systematic review of all existing data sets. We will display examples for some therapeutics that have been evaluated in an evidence based approach, resulting in changing attitudes towards their use.

6.2.1 Hormone Replacement Therapy: WHI study

Hormone replacement therapy, (HRT) involves the replacement of the depleted hormone levels in menopausal women by the administration of synthetic estrogen with or without progestogen with the aim to alleviate symptoms of menopause.

Despite the potential health benefits that were expected from the use of HRT, many risks and complications have been associated with its use. Although observational studies suggested protective effects on heart disease (Stampfer *et al*., 1991), osteoporosis (Lindsay *et al*., 1976), and even Alzheimer's disease (Henderson *et al*., 1994), recent clinical trials have questioned some of these benefits. Till now, the debate regarding the risk-benefit ratio of hormone replacement therapy has not been completely resolved.

However, in July 2002, the Women's Health Initiative (WHI), - a large, multicentric clinical trial by the National Heart, Lung and Blood Institute (NHLBI) and other units of National Institute of Health (NIH) – reported that hormone replacement therapy actually posed more health risks than benefits (Rossouw *et al*., 2002).

This was **the turning point** in HRT, as the number of health hazards attributed to HRT grew, practitioners discontinued routine prescriptions for this once a time very popular and rampant treatment modality and HRT use substantially decreased in the general population (Dorval *et al*., 2007, Hersh *et al*., 2004, Majumdar *et al*., 2004).

The results of this study provide the best evidence available at present on HRT for prevention of heart disease, and indicate that combined HRT is not indicated for this purpose in the studied population, thus contradicting the reported beneficial effects of HRT on coronary heart disease (CHD) in previous observational studies (Rossouw *et al*., 2002).

6.2.2 Inudction of ovulation in patients with polycystic ovary syndrome

Polycystic ovary syndrome has an estimated prevalence of 4-8 % in reproductive-aged women (Knochenhauer *et al*., 1998; Asuncion *et al*., 2000). It is the most common cause of oligoanovulatory infertility (Hull, 1987). Ovulation in these cases has been suggested to be induced by the use of clomiphene citrate or insulin sensitizer or combination of both.

Metformin as an insulin sensitizer improves peripheral insulin sensitivity by decreasing glucose production by the liver and increasing the sensitivity of target tissues to insulin. Metformin was also found to reduce levels of androgens in both lean and obese women, leading to increased rates of spontaneous ovulation (Batukan *et al*., 2001; Haas *et al*., 2003; Essah *et al*., 2006).

It has been demonstrated by a number of studies that up to 40 % of anovulatory women with polycystic ovary syndrome will ovulate, and many will achieve pregnancy with metformin alone (Diamanti-Kandarakis *et al*., 1998; Neveu *et al*., 2007).

Despite the postulated effectiveness of metformin in induction of ovulation in cases with polycystic ovary syndrome, randomised controlled trials conducted by Moll et al., 2006 and Legro et al., 2007 didn't support these expectations.

Moll *et al*., 2006 performed a randomised double blind clinical trial to compare the effect of clomiphene citrate plus metformin and clomiphene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome. The authors recruited 228 women with polycystic ovary syndrome, of those, 111 women were allocated to clomiphene citrate plus metformin (metformin group) and 114 women were allocated to clomiphene citrate plus placebo (placebo group).

The results of the study showed that the ovulation rate in the metformin group was 64% compared with 72% in the placebo group, a non-significant difference (risk difference − 8%, 95% confidence interval − 20% to 4%). Hence, the authors concluded that metformin is not an effective addition to clomiphene citrate as the primary method of inducing ovulation in women with polycystic ovary syndrome.

The above conclusion was also emphasized by another study performed by Legro *et al*. in 2007 who conducted a randomized prospective study involving 626 infertile women with polycystic ovary syndrome. In this study, the authors found live-birth rates with clomiphene citrate alone were higher (22.5 %) than with metformin alone (7.2 %) (Legro *et al*., 2007).

6.2.3 Metformin in prevention of ovarian hyperstimulation syndrome

Ovarian hyperstimulation syndrome (OHSS) is considered to be the most serious complication of superovulation in IVF-embryo transfer. The syndrome can vary in presentation from mild to severe life threatening disease. Severe manifestations of OHSS may include massive fluid shifts, hemoconcentration or renal and liver dysfunction. The

syndrome may be ultimately complicated by thromboembolic events and adult respiratory distress syndrome (Rizk and Aboulghar, 1999).

Several strategies have been suggested to prevent such life threatening complication of ovulation induction. Among the suggested strategies is the administration of metformin. A **meta-analysis** has indicated that the administration of metformin significantly prevents OHSS development in patients with polycystic ovary syndrome, a high risk group (Costello *et al*., 2006).

The mechanism of action of metformin is not completely clear, but both reduction of ovarian reserve, as demonstrated by the reduction of anti-Müllerian hormone (AMH) values (Piltonen *et al*., 2005), and a reduced insulin dependent VEGF production (Tang *et al*., 2006), have been suggested.

6.2.4 Changing attitudes in ovarian stimulation towards patient's safety

Gonadotropin-releasing hormone agonists (GnRHa) were introduced in ovarian stimulation for IVF to suppress the premature surge of luteinizing hormone (LH).

Various protocols have been suggested for controlled ovarian hyperstimulation in assisted reproduction, however, the long agonist protocol have been the standard protocol because of the associated increase in pregnancy rates.

In this long agonist protocol, GnRHa is started either in the mid-luteal phase or in the early follicular phase of the preceding cycle and continued until pituitary desensitization has been achieved; usually after 2–3 weeks, at which point gonadotropin administration will be started (Al-Inany and Aboulghar, 2003).

However, despite the increased pregnancy rates, the use of the GnRHa long protocols has been concurrently associated with an increase in the incidence of ovarian hyperstimulation syndrome (Rizk and Smitz, 1992).

The fear from such serious and potentially life threatening complications has motivated researchers to study other alternative protocols that would achieve better safety with at least equivalent results, thus improving the outcome of IVF. Gonadotropin-releasing hormone antagonists have emerged as an alternative treatment for preventing premature LH surges during controlled ovarian hyperstimulation (Al-Inany *et al*., 2011).

GnRH agonist and antagonist exert their effects through different mechanisms of action. GnRH agonists act by downregulation of pituitary GnRH receptors and desensitization of the gonadotropic cells, while GnRH antagonists act by directly and rapidly inhibiting gonadotropin release within several hours through competitive binding to pituitary GnRH receptors. This mechanism of action is dependent on the equilibrium between endogenous GnRH and the applied antagonist and is highly dose dependent in contrast to the agonists (Felberbaum *et al*., 1995).

The competitive blockade of the receptors by GnRH antagonists results in immediate arrest of gonadotropin secretion; therefore, they can be given after starting gonadotropin administration. This will lead to dramatic reduction in the duration of treatment cycle as well as avoiding flare up and estrogen deprivation symptoms associated with GnRHa-induced downregulation.

Cochrane reviews comparing GnRH antagonist to the more widely used long GnRH agonist protocols were published successively, with the first review published in 2001 (Al-Inany and Aboulghar, 2001), that was later updated in 2006 (Al-Inany *et al*., 2006) and recently updated again in 2011 (Al-Inany *et al*., 2011). The last updated review focused on patient-oriented value mainly safety and ongoing pregnancy/live birth rate.

The earlier two versions of that review showed lower efficacy for GnRH antagonists while the most recent one showed lower pregnancy in antagonist but did not reach statistically significant level.

According to the most recent review, nine trials reported live birth rates in 1515 women. There was no significant difference in live birth rates following GnRH antagonist compared with GnRH agonist (OR = 0.86, 95% CI = 0.69 to 1.08; p = 0.20; I^2 = 0.00%, 95% CI = 0.00% to 31.62%) (Figure 3).

However, more importantly, there were a statistically highly significant lower incidence of OHSS in the GnRH antagonist group (Twenty-nine randomized controlled trials reported ovarian hyperstimulation rates in 5417 women, R.D = -0.03, 95% CI = -0.05 to -0.02; p < 0.00001; I2 = 67,68%, 95% CI = 52.50% to 78.02%) (See Figure 4).

Thus, there was a significant difference favouring GnRH antagonist compared with GnRH agonist. The incidence was reduced by 50% in antagonist group (1.91 vs 3.74%). The corresponding number needed to harm was 25 (95% CI: 19–36) with an absolute risk reduction of 4% (95% CI: 2.79–5.13).

This means that for every 25 women undergoing downregulation by agonist, one more case of severe OHSS may be expected. In addition, the cancellation rate owing to high risk to develop OHSS was significantly higher in GnRHa group. This means that the difference would be highly significant if cancellation was not done (Al-Inany *et al*., 2011).

6.2.5 For intrauterine insemination (IUI) timing: Which is the best; human chorionic gonadotropin administration or monitoring of LH surge?

Kosmas *et al*., 2007 conducted a systematic review and meta-anlaysis to find out whether the timing of intrauterine insemination by the administration of hCG achieves better results than the monitoring of LH surge.

Seven studies with 2,623 patients were involved in this meta-analysis, in which 1,461 patients received hCG, and 1,162 had LH surge detection. When all studies were combined, patients who received hCG before IUI demonstrated lower clinical-pregnancy rates than did women who had IUI after spontaneous ovulation (odds ratio, 0.74; 95% confidence interval, 0.57–0.961).

In subgroup analysis of studies that considered ovulatory dysfunction to be the infertility reason, the results favored women who received hCG. In contrast, across studies that reported male factor as the infertility reason, as well as across studies including women with unexplained infertility, results appeared to favor the LH surge detection approach. However, none of those subgroup analyses reached statistical significance (Kosmas *et al*., 2007).

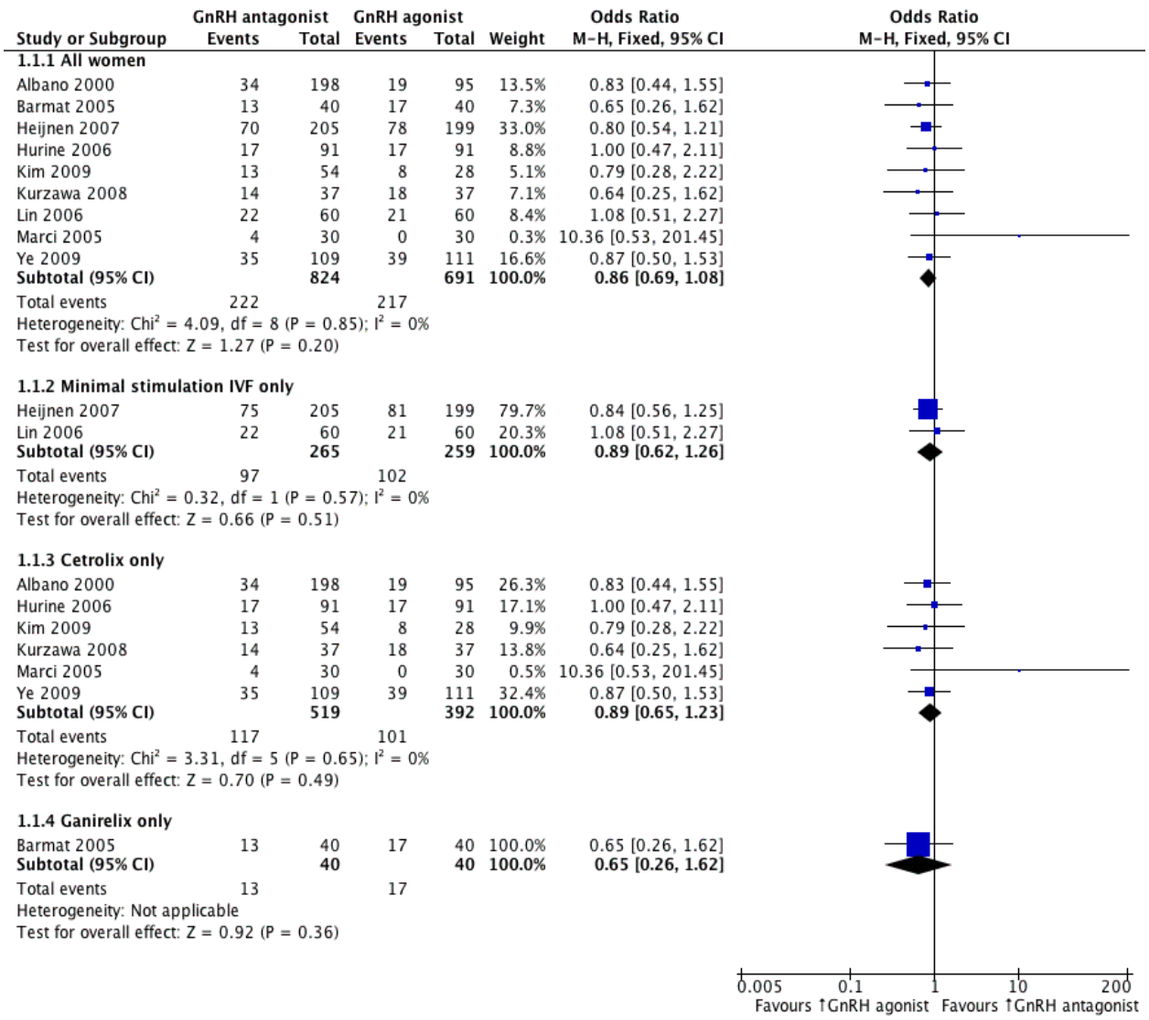

Fig. 4. Forest plot of comparison: GnRH antagonist Vs GnRH agonist live birth rate per women randomized

6.3 Changing attitudes towards diagnostics (evidence based diagnosis)

Evidence-based medicine has progressively developed as the standard approach for many diagnostic procedures. With the increasing varieties of investigating and diagnostic tools, evidence based medicine allows for the selection of the best diagnostic approach that would achieve the most reliable diagnosis with the least possible expenses, thus avoiding other less accurate and unnecessary diagnostic methods.

6.3.1 Anti-Müllerian hormone

Anti-Müllerian hormone (AMH) has become the 'molecule of the moment' in the field of Reproductive Endocrinology. Indeed, it is valuable as a means of increasing understanding of ovarian pathophysiology and for guiding clinical management across a broad range of conditions.

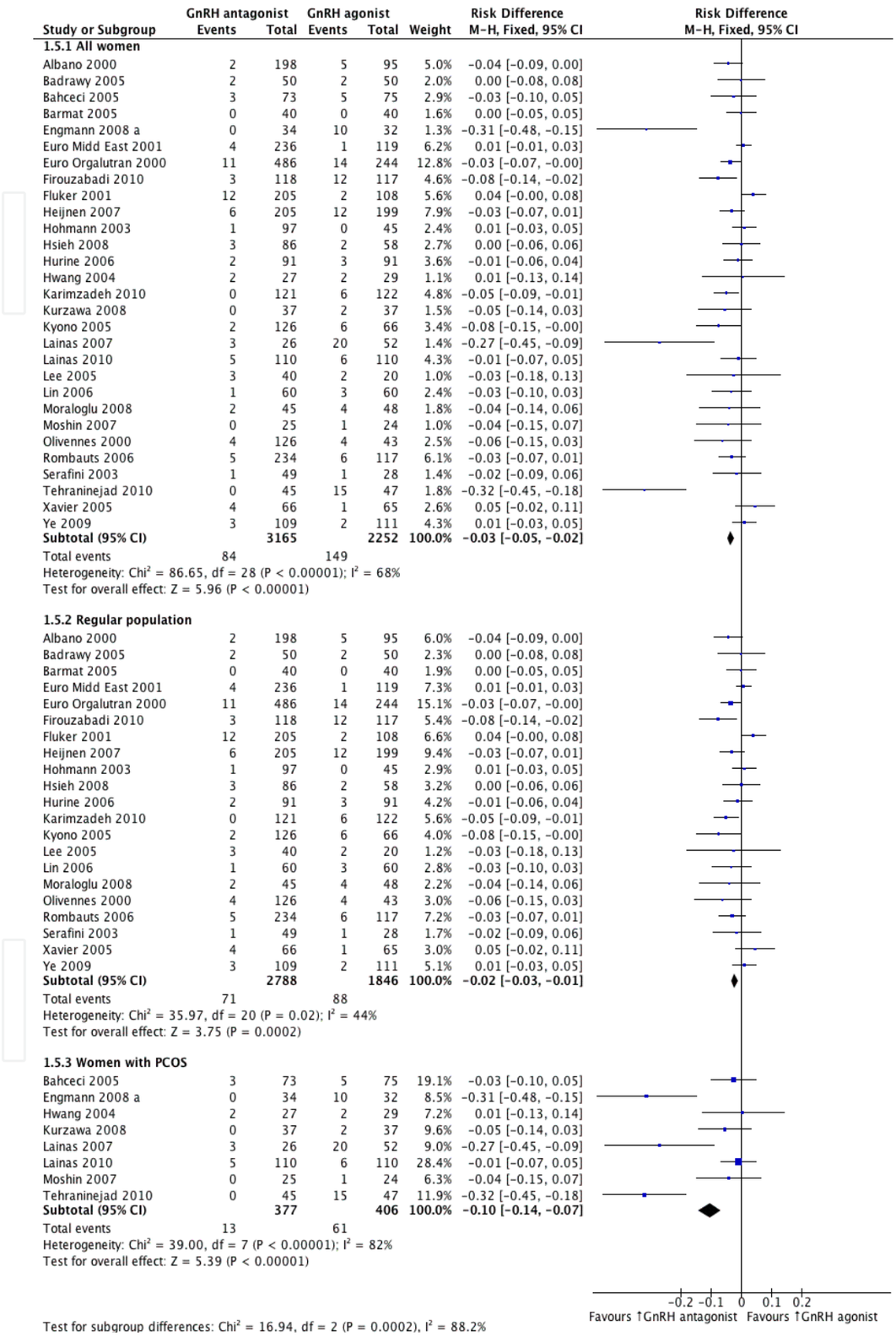

Fig. 5. GnRH antagonist vs GnRH agonist ovarian hyperstimulation per women randomised

In a cross-sectional study by La Marca *et al*., 2010, AMH was measured in 277 healthy females (aged 18–50 years) by commercial enzyme-linked immunosorbent assay. Serum AMH concentrations show a progressive decline with female ageing. The age-related changes in AMH were best fitted by a polynomial function. Mean AMH concentrations were not modified by past use of oral contraceptive and were independent of parity of women. Age-specific normative values for circulating AMH concentration were established. AMH concentrations seem to be independent of the reproductive history of the patient (La Marca *et al*., 2010).

AMH plays a basic role as a prognostic marker in women undergoing ovarian stimulation protocols and can predict an excessive response to ovarian stimulation (Broer *et al*., 2010).

7. Conclusions

Evidence Based Medicine is currently changing our daily practice in obstetrics and gynecology towards achieving better health to women and mothers all over the world. The best evidence can be extracted from clinically relevant research that answers a clinical question using sound methodology.

Our paradigms in the fields of diagnosis, interventions and therapeutics have exhibited some of the progress that has been performed throughout the last years. There is an increasing necessity for systematically reviewing, appraising and using clinical research findings to shift our practice towards an evidence based one. Evidence-based practice requires a clear view of the evidence combined with wise integration of this information with other knowledge and experience in clinical decision making.

Evidence based medicine has been adopted, alongside health economics, and has been promoted as the gold standard tool for advancement and provision of health services in obstetrics and gynecology. Thus, a keen and sincere physician should be seeking evidence based medicine and integrating evidence based practice to deliver a higher level of health service to his patients.

In a domain full of controversies as that of the obstetrics and gynecology, it is crucial to consider what the evidence says and exert every effort to integrate this evidence into practice as this will be the surest way that a patient will receive safe and effective up to date health service.

Drawing examples on evidence based medicine is endless and can not be fulfilled completely in this context however, we aimed to draw the light on the role of evidence based medicine in changing attitudes in our routine daily practice by demonstrating some important examples that would emphasize that role.

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Evidence-based medicine (EBM) was introduced to the best benefit of the patient. It has transformed the pathophysiological approach to the outcome approach of today's treatments. Disease-oriented to patient-oriented medicine. And, for some, daily medical practice from patient oriented to case oriented medicine. Evidence has changed the paternalistic way of medical practice. And gave room to patients, who show a tendency towards partnership. Although EBM has introduced a different way of thinking in the day to day medical practice, there is plenty of space for implementation and improvement. This book is meant to provoke the thinker towards the unlimited borders of caring for the patient.

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