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Review

Standards of Care in infertility in Europe

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ABSTRACT

Evidence-based medicine is the principal approach to medical practice. There are several debatable issues in infertility, which require clarification. Over the past 20 years, reliable methodology has been developed for the management of infertile couples. This includes high quality diagnostic and therapeutic procedures, which are applied in highly specialised infertility centres. The European Board and College of Obstetrics and Gynaecology (EBCOG) has published Standards of Care for Women's Health in Europe, which should be the cornerstone for the clinicians and service providers in the European Union to establish common protocols within their centres. Each infertility treatment should result in the highest possible success rate and all appropriate measures for the patient's safety should be in place. The treatment protocols should minimise risk of complications, such as ovarian hyperstimulation syndrome (OHSS). The current use of GnRH agonists to trigger final follicle maturation has provided the means for avoiding this syndrome. Additionally, multiple pregnancy rates are still high in assisted reproductive technology (ART). These rates should be reduced by the adoption of single embryo transfer during IVF treatment and by the proper monitoring of ovulation induction protocols. EBCOG Standards of Care for infertility and assisted conception treatment derived from the best available evidence should underpin the provision of high quality infertility services in European countries.

Contents

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Introduction

Infertility is the inability of a couple to conceive after at least 12 months of regular unprotected intercourse. In the past, treatment of infertility was predominantly empirical, while nowadays, it is mainly delivered using evidence-based recommendations. In-vitro fertilisation (IVF) and intra-cytoplasmic sperm injection (ICSI) have dramatically changed the treatment of infertility. A proper infertility work-up guides the way towards an aetiological and cost-effective approach. For example, induction of ovulation is the first-line treatment in anovulatory infertility [1]. When infertility is related to tubal disease, the majority of the cases are now treated by IVF, in preference to the "hi-tech" microsurgery that used to be the method of choice in the past [2]. It should be noted, however, that overuse of IVF outside specific indications might not be a cost-effective procedure. Available algorithms and nomogrammes provide help to the clinicians in selecting the appropriate method for infertility treatment according to current evidence and technology. In this review, various debatable issues related to infertility management will be discussed in the context of an evidence-based approach.

Clinical evidence

Anovulation/ovulation induction

Anovulation is the cause of female infertility in about 25% of the cases. According to World Health Organization (WHO), anovulation is classified into four categories, i.e. hypogonadotrophic hypogonadism (WHO group I), normogonadotrophic hypogonadism (WHO group II—polycystic ovary syndrome-PCOS), hypergonadotrophic hypogonadism (WHO group III—ovarian insufficiency) and hyperprolactinaemia.

Ovulation induction is the best approach for treating infertility in all these cases except in those with ovarian insufficiency, which should be managed in the context of an IVF oocyte donation programme. Hyperprolactinaemia, either idiopathic or due to a pituitary adenoma, is treated with the use of dopaminergic agents.

For hypogonadotrophic hypogonadism, ovulation induction is attempted with the use of human gonadotrophins [3]. As both FSH and LH are required for normal folliculogenesis, these two gonadotrophins should be given together from the beginning of ovarian stimulation. Literature lacks prospective randomised trials and the evidence is derived only from old retrospective studies. According to these studies, multiple pregnancy rates are very high, exceeding 30% in the majority of them [1]. These rates can be reduced with proper monitoring, but prospective randomised trials are required. Pulsatile GnRH is an alternative treatment and it is used provided that the pituitary is intact. With that kind of treatment, multiple pregnancy rates are very low [4].

In WHO group II, a specific algorithm is used, based on the Thessaloniki consensus meeting on infertility management of PCOS organised by ESHRE/ASRM in 2007 [5]. First-line treatment is the use of the anti-oestrogenic compound, clomiphene citrate, given for up to 6 treatment cycles. In case of clomiphene failure or clomiphene resistance, a second-line treatment is applied including the use of low-dose protocols of FSH, i.e. the step-up and the step-down. Laparoscopic ovarian drilling competes with FSH as a second-line approach, but it is used only in the presence of specific indications. Alternative treatments include aromatase inhibitors, such as letrozole, but these drugs, although effective as first-line approach [6], are "off-label" for infertility treatment. Finally, the insulin sensitiser, metformin, is in use, but this is not considered an ovulation-inducing agent. Metformin, however, can be helpful only in clomiphene resistant patients in combination with clomiphene and before moving to a FSH low-dose protocol [7].

GnRH agonist triggering vs. Human Chorionic Gonadotrophin (HCG)

Ovarian hyperstimulation syndrome (OHSS) can be a serious complication of ovarian stimulation for IVF. It can also occur during ovulation induction, but with proper monitoring and the application of low-dose FSH protocols, the incidence is very low. It has been shown that in IVF cycles, live birth rate increases in proportion to the number of collected oocytes [8]. Although the optimal number of oocytes for a safe and successful procedure has not been defined, with the use of mild ovarian stimulation protocols, a relatively small number of oocytes is available for collection, making OHSS a rare event. Nevertheless, in order to reduce the cost of repeated oocyte retrievals, the recovery of many oocytes in one shot and the creation of multiple embryos for transfer in subsequent frozen cycles have become a reality. Recent evidence derived from the prospective randomised clinical trials has shown that in hyperstimulated cycles, the use of a GnRH agonist instead of HCG for triggering final oocyte maturation dramatically reduce the incidence of OHSS [9]. Although luteal phase support may rescue the cycle under these conditions [10], cryopreservation of all embryos ("freeze all" technique) for transfer in subsequent frozen cycles is a safe option [11].

IVF vs. ICSI

IVF is a well-established method for the treatment of infertility. Although IVF was first introduced for the treatment of women with tubal factor infertility, very soon the list of indications was expanded to include cases that failed to achieve a pregnancy with more suitable methods. Patients with male factor infertility are now treated with ICSI. The indications of ICSI have also expanded to include non-male infertility as well as recurrent fertilisation failure during IVF treatment. A recent meta-analysis has shown that ICSI, as compared to IVF, increases the fertilisation rate in women with unexplained infertility, but the impact on pregnancy and live birth rates was not addressed [12]. In women with endometriosis, ICSI offers a higher fertilisation rate and a lower rate of total fertilisation failure compared with IVF but there was no difference in pregnancy and implantation rates [13]. Large prospective randomised trials are required to assess the role of ICSI in non-male infertility.

Intrauterine insemination (IUI)

Intrauterine insemination (IUI) is meant to overcome the problems related to decreased sperm potential. Various semen parameters affect the clinical outcome following IUI, but further prospective trials are needed [14]. In terms of the synchronisation technique of ovulation and IUI, little information exists to draw firm conclusions [15]. Preliminary analysis of published studies has demonstrated that treatment with gonadotrophins of men suffering from idiopathic subfertility may increase the possibility of a pregnancy and live birth [16]. However, large prospective randomised trials are needed to investigate this matter further. In unexplained infertility, although IVF provides a higher live birth rate than IUI in unstimulated cycles, there is no conclusive evidence that IVF is better than IUI plus gonadotrophins or IUI plus clomiphene [17].

GnRH agonists vs. GnRH antagonists

GnRH analogues (agonists or antagonists) are used during ovarian stimulation for IVF in order to prevent the occurrence of premature LH surge. The agonists are very effective in preventing the LH surge [18], while with the antagonists several LH peaks may take place during the ovarian stimulation [19]. Despite this, clinical outcome does not differ significantly between agonists and antagonists. Earlier studies had shown a 5% difference in live birth rates in favour of the agonists. Nevertheless, recent meta-analyses have shown that, although the pregnancy rate can be higher with the agonists, the live birth rate is similar [20,21]. In all studies, the comparison has been made between a long GnRH agonist protocol and a GnRH antagonist protocol (always short). The clinical pregnancy rate seems to be higher in the long GnRH agonists protocol than the short protocol (moderate quality evidence) [22]. In terms of OHSS, there is evidence of a significantly lower incidence in the short antagonist protocol as compared to long agonist protocol [23]. The recent Cochrane systematic review [21] suggests that the risk reduction of OHSS without reducing the likelihood of achieving live birth with the antagonists is moderate.

LH supplementation

Pituitary LH is very important for normal folliculogenesis. This hormone contributes to normal follicle maturation during the follicular phase of the cycle by stimulating androgen production from the theca cells and supporting further growth of the selected dominant follicle. In superovulated cycles for IVF, supra-physiological concentrations of oestradiol suppress the secretion of LH from the pituitary via the negative feedback [24]. As a result, serum LH levels are markedly reduced. It has been shown that in unselected population of women undergoing IVF treatment, supplementation with exogenous LH during ovarian stimulation with FSH does not have any beneficial effect and is not recommended [25,26]. In contrast, in poor ovarian responders, evidence has been provided that clinical pregnancy and ongoing pregnancy rates increase with the addition of exogenous LH, but the live birth rate is not affected [27]. Since the evidence is of low quality, further randomised trials are needed. The only group of women requiring LH together with FSH for ovarian stimulation is that of hypogonadotrophic hypogonadism [28].

Luteal phase support

Normally, after ovulation, the formation of the corpus luteum takes place, which produces progesterone. The role of this hormone is to prepare endometrial receptivity for embryo implantation. LH is the main luteotrophic hormone in women. During assisted reproduction, the ovarian stimulation process via the high concentrations of oestradiol and progesterone suppresses LH levels leading to a defective luteal phase. Thus, medical support for this phase is needed [29]. Progesterone administration during the luteal phase results in an improvement of live birth or ongoing pregnancy rates as compared to placebo. Also, administration of HCG increases significantly the live birth rate and ongoing pregnancy rate than placebo. The addition of oestrogen to progesterone does not provide any benefit. The administration of a GnRH agonist together with progesterone seems to improve the outcomes. Oral dydrogesterone is as effective as vaginal progesterone [30,31], thus the route of progesterone administration is not associated with an improvement in outcomes.

Blastocyst vs. cleavage stage embryo transfer

Embryo transfer is performed either at an early stage during cleavage (days 2–3) or at the blastocyst stage (days 5–6). However, it is not robustly known which of the two stages described above provides better clinical outcome as the most recent Cochrane systematic review has concluded that the evidence level is low with fresh embryo transfer at the blastocyst stage, and the live birth rate is significantly higher than at cleavage stage. It was suggested that if 29% of women would achieve live birth after transfer at cleavage stage, the rate of live birth after blastocyst transfer would be between 32% and 42% [32]. This difference, however, did not seem to influence the cumulative pregnancy and live birth rates. Because of the low level of evidence, large randomised controlled trials are needed.

Endometrial scratching

This novel approach to the management of recurrent implantation failure suggests that injuring the endometrium during the cycle preceding the embryo transfer cycle results in a 70% higher possibility of achieving a pregnancy as compared to no treatment or more likely to achieve a pregnancy as compared to endometrium evaluation only with the hysteroscope [33]. In asymptomatic women, hysteroscopy performed prior to their first IVF cycle increases the likelihood of pregnancy and live birth [34]. Nevertheless, a recent meta-analysis has provided very low or mederate quality evidence that hysteroscopy preformed before an IVF/ICSI treatment in women with no uterine abnormalities increases pregnancy and live birth rates [35]. Large prospective randomised trials are needed.

Fibroids and polyps

Fibroids, also called myomas or leiomyomas, are the commonest tumours of the uterus. Their role in infertility is still unclear. Removal of submucus fibroids at hysteroscopy will increase the possibility for a successful outcome of pregnancy [36]. The same was also true for endometrial polyps before IUI [36]. As regards to women with intramural fibroids not distorting the endometrial cavity, they tend to have lower pregnancy and live birth rates following IVF as compared to women without fibroids [37]. Even tumours $\leq$4 cm in diameter may affect the outcome of treatment especially if the distance of the tumour from the endometrium is $\leq$1 cm, then the implantation rate is lower [38]. Nevertheless, there is no evidence to recommend removal of intramural fibroids in women with otherwise unexplained infertility and intact endometrium. On the contrary, there is evidence (II-2D) against myomectomy in such cases

regardless of the size of the fibroid [39]. Treatment should possibly be individualised (III-C).

Endometriosis

Endometriosis is common in infertile women. The presence of endometriosis of stage I/II is associated with decreased fertilisation and of stage III/IV with decreased implantation and pregnancy rates [40].

However, a recent meta-analysis showed no difference in live birth rate and in clinical pregnancy rate between women with and without endometriosis. This remained unchanged after surgery, although the number of oocytes retrieved decreased and the cycle cancellation rate was increased in women with endometriosis undergoing IVF treatment [41]. Whether endometriomas should be removed before IVF is a matter of debate. Surgical excision of endometriomas further reduces ovarian reserves as assessed by antimullerian hormone (AMH) measurement and antral follicle count [42–44], and surgery does not improve IVF outcomes [45]. However, it is recommended that the endometriomas >4 cm in diameter should be removed as the pregnancy rate following ovarian cystectomy is increased [46].

Antioxidants

Oxidative stress may have an impact on sperm quality and possibly on sperm fertilising capacity. There is low quality evidence to suggest that the use of antioxidants by subfertile males may increase clinical pregnancy and live birth rates [47]. Similarly in females, the evidence is of very low quality, of no increase in pregnancy and live birth rates when antioxidants are used [48].

Androgens in poor responders

Androgens (DHEA or testosterone) are physiological precursors of oestrogens during ovarian steroidogenesis. In poor responders undergoing IVF, pre-treatment with testosterone or DHEA may improve live birth rate but the evidence is moderate [49]. A recent randomised clinical trial showed that in poor responders, testosterone during ovarian stimulation in a long agonist protocol failed to increase the number of oocyte-cumulus complexes as compared to no treatment [50]. Further randomised trials are needed to clarify the issue.

Hydrosalpinx

Hydrosalpinx may have a deleterious effect on embryo implantation. Surgical intervention, either as proximal tubal occlusion or salpingectomy, has a beneficial effect on subsequent IVF treatment [51]. Tubal occlusion seems to be more effective than salpingectomy. Hysteroscopic application of intratubal devices, such as Essure, is also effective but inferior to laparoscopic salpingectomy in terms of ongoing pregnancy rate [52]. The Essure tubal occlusion hysteroscopically increases the miscarriage rate as compared to other interventions [53].

Fresh vs. frozen embryo transfer

Ovarian hyperstimulation for IVF induces marked changes in the endocrinology of the menstrual cycle, which can have an impact on endometrium maturation. This may influence clinical outcome after embryo transfer. In a recent meta-analysis, it was shown that clinical pregnancy and ongoing pregnancy rates were higher in cycles with frozen as compared to cycles with fresh embryo transfer [54].

Summary of evidence

In this review, current infertility management based on the most recent systematic reviews and meta-analyses has been presented. These reviews include evidence, mainly derived from randomised clinical trials, but they also include retrospective, non-randomised studies or those with small number of cases. Although the number of meta-analyses is increasing rapidly, the evidence can occasionally be of low quality or inadequate to provide valid information. Additionally, different meta-analyses may provide different or even opposite results on the same subject.

This review provides adequate evidence in some areas such as: the use of GnRH agonists instead of HCG for triggering final oocyte maturation, the clinical effectiveness of GnRH agonists and antagonists, the luteal phase support, the effectiveness of IVF and ICSI, the use of gonadotrophins for ovulation induction, the surgical occlusion of the tubes/removal in women with hydrosalpinges, the transfer of frozen–thawed embryos etc. However, there are unresolved issues including the role of endometrial scratching, the surgical management of endometriosis, the management of fibroids and endometrial polyps, the pretreatment with androgens in poor responders, the supplementation with LH in poor responders and the use of antioxidants for the management of male or female infertility.

Successful infertility treatment, apart from being cost-effective, should also provide a high success rate, while all safety measures should be taken. Poorly regulated assisted conception treatments, IVF and ICSI together with ovulation induction can be dangerous for the patient, as they can result in serious complications; the two most important complications of ovarian stimulation are OHSS and multiple pregnancies. The evidence provided above indicates that this syndrome can be markedly reduced when final oocyte maturation is triggered via the administration of a GnRH agonist instead of HCG [9]. Cryopreservation of all embryos and arrangement of embryo transfer in subsequent natural cycles seem to be effective [11]. In such cycles, endometrium maturation is expected to be closer to the physiology and better synchronised with the stage of embryo development, while in hyperstimulated cycles endometrium maturation is disturbed, advanced or even occasionally delayed [55]. Furthermore, the transfer of cryopreserved-thawed embryos results in higher clinical and ongoing pregnancy rates than the transfer of fresh embryos [54].

Multiple pregnancies are a common complication during IVF treatment [56]. It is evident that the occurrence of multiple pregnancies is directly related to the number of embryos transferred, since the possibility of homo-zygotic twins or triplets after single embryo transfer is very low [57,58]. Although a twin pregnancy could be acceptable as saving the patient from multiple IVF attempts and the burden of more than one pregnancy, there are several disadvantages particularly related to prematurity, which may not make it a cost-effective solution [59,60]. Within Europe, there are no uniform policies on the number of embryos which can be transferred. EBCOG's position statement [61] recommends single embryo transfer as it has been shown that the transfer of one fresh embryo in one cycle and one cryopreserved embryo in a subsequent cycle, if required, gives the same live birth rate as the transfer of two embryos at the same time [62,63]. Based on the fact that cryopreservation via the use of vitrification is a very efficient methodology, single embryo transfer is an effective procedure for the benefit of the mother and the baby and it is undoubtedly recommended [61].

The chance of the delivery of a healthy baby is almost five times more likely with single embryo transfer. Multiple pregnancies can also occur following ovulation induction in women with anovulatory infertility [64]. It is therefore recommended that closer monitoring of the ovarian stimulation with the use of vaginal

ultrasound scans and serum oestradiol measurement together with strict criteria for the HCG administration be implemented uniformally. The situation is different in cases of anovulation related to PCOS, in which the use of low-dose FSH protocols has restricted multiple pregnancies to less than 10%, which are mostly twins [65,66].

Standards of Care

The European Board and College of Obstetrics and Gynaecology (EBCOG) is a representative body of 37 European National Societies of Obstetrics & Gynaecology. EBCOG is responsible for streamlining post-graduate training and also sets Standards of Care in Europe. EBCOG launched two documents describing Standards of Care in Obstetrics & Gynaecology, including infertility [67]. The purpose of setting standards is to streamline the care of women and reduce variation in the quality of care across Europe. Each standard is supported by an auditable indicator to collect standardised data for inter centre and intra/inter country comparison for defined outcomes. While it is not possible to reproduce the full text of "*EBCOG Standards of Care for Infertility and Assisted Conception—Chapter 19*", we are highlighting an abbreviated version [67].

The standards bring clarity about the rights of the couple, openness to information as regards to treatment choices available, couple focused treatment plan, access to counselling, and the availability of data on success rates for each treatment modality in an easily understandable language, without the use of medical jargon.

The standards also expect that all principles of clinical governance should be adhered to as regards confidentiality, record keeping, laboratory facilities, gamete handling and evidence based protocols. The laboratory should meet all the standards as set out in the European Union Tissues and Cells Directives (first Directive 2004/23/EC).

EBCOG further recommends that the process, specific protocols for investigation and treatments for assisted conception including ovulation induction should be in place. Treatment protocols should be based on evidence, and clinical outcome should be regularly collected and reviewed in the context of an audit process. Each centre should use protocols to avoid complications of treatment, such as OHSS and multiple pregnancies. Single embryo transfer must be considered by all European IVF Centres. Furthermore, as regards to gametes donation: legal, social and cultural issues should be taken into account with the appropriate professional counselling.

The document also provides guidance on the staffing of the treatment centres and also sets out "Training Standards" for the future generation of specialists in Obstetrics and Gynaecology. Although the standards should be the basis for the provision of high quality infertility services, there should be flexibility and on occasions, individualisation of management may apply.

Conclusions

There remains considerable inequitable access and variable outcomes in the area of assisted conception and induction of ovulation. We have provided evidence in all areas of clinical practice. We are seriously concerned about the higher rates of multiple pregnancies in many hot spots within Europe. EBCOG strongly believes that infertility care provision should be based on evidence derived from prospective randomised clinical trials. Premature deliveries are associated with huge costs for already over stretched local advanced neonatal services and to the society [68]. EBCOG strongly advocates that emerging evidence should lead to the development of proper guidelines for the management of infertility, in order to not only reduce treatment related complications but also to address the huge challenge of multiple pregnancies [61]. EBCOG's recommendations should be used to develop common standards of infertility care for all European countries where comparative data can be collected and bench marked. Finally, EBCOG recommends that more appropriately sized randomised clinical trials, funded by the European Union, are needed to delineate the role of various conditions in disturbing reproductive function and to provide the means for their treatment.

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Conflicts of interest

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