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REVIEW ARTICLE

Anovulation and ovulation induction

Katsikis I, Kita M, Karkanaki A, Prapas N, Panidis D

Division of Endocrinology and Human Reproduction, 2nd Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki, Greece

Abstract

Conventional treatment of normogonadotropic anovulatory infertility is ovulation induction using the antiestrogen clomiphene citrate, followed by follicle-stimulating hormone. Multiple follicle development, associated with ovarian hyperstimulation, and multiple pregnancy remain the major complications. Cumulative singleton and multiple pregnancy rate data after different induction treatments are needed. Newer ovulation induction interventions, such as insulin-sensitizing drugs, aromatase inhibitors and laparoscopic ovarian electrocoagulation, should be compared with conventional treatments. Ovulation induction efficiency might improve if patient subgroups with altered chances for success or complications with new or conventional techniques could be identified, using multivariate prediction models based on initial screening characteristics. This would make ovulation induction more cost-effective, safe and convenient, enabling doctors to advise patients on the most effective and patient-tailored treatment strategy. *Hippokratia 2006; 10 (3): 120-127*

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Corresponding author: *Katsikis I, 4A, Stratigou Kallari Str. 54622, Thessaloniki, Greece, tel. +30 2310 268 532, e-mail: ilkats@otenet.gr*

Going back in history

Until the early 1960s efficient treatment of anovulation was virtually non existent. To couples who consulted us because they did not succeed in achieving a pregnancy we would offer only psychological support, explanation of proper technique and frequency and timing of intercourse and, in some countries, artificial donor insemination for cases of severe male infertility.

During the 1960s and 1970s a veritable avalanche of drugs, methods and modalities for effective treatment of infertility, particularly of anovulation, came, also simultaneously, from several directions.

In 1961, Greenblatt et al[1] published the first results achieved by application of clomiphene citrate (MRL-41). Since then, thousands of anovulatory women have been able to enjoy maternity thanks to this simple, cheap and relatively safe treatment.

Gemzell et al announced the first successful induction of ovulation using human pituitary gonadotropins in 1958[2], and the first pregnancy in 1960[3]. One year later, Bettendorf et al[4] reported on similar experience. Both Gemzell and Bettendorf were also able to achieve pregnancies in hypophysectomized patients by application of human pituitary gonadotropins[5,6], a feat which was certainly a major breakthrough.

Concomitant with these efforts, Lunenfeld et al[7] succeeded in extracting a potent gonadotropin material from the urine of menopausal women and showed that this preparation enabled the induction of ovulation and pregnancy in a large series of amenorrhoeic women[8,9].

During the 1970s, two additional modalities for treatment of anovulation were introduced-gonadotropin-releasing hormone and prolactin-inhibiting agents.

The gonadotropin-releasing hormone (GnRH) was isolated, its structure established[10-13], and shortly afterwards a preparation of native GnRH, synthesized in the laboratory, was made available for clinical use. It took several years until Knobil, in 1980[14], showed that in order to be effective, GnRH must be applied not continuously but in pulses precisely spaced in time. Indeed, the pulsatile GnRH therapy proved to be very effective in inducing ovulation and pregnancy in women who suffered from hypogonadotrophic amenorrhoea of hypothalamic origin[15,16].

Prolactin, a peptide secreted by the pituitary gland was purified a year later[17]. In the same year, a specific assay for human prolactin was made available[18], and this made it possible to show that excessive secretion of prolactin might result in impaired pulsatility of LH discharge and cause amenorrhoea or anovulation with or without galactorrhoea[19,20]. During a 3-year period, between 1974 and 1977, a number of publications appeared which showed unequivocally that bromocryptine (a lysergic acid derivative) is efficient in reducing the circulating levels of prolactin and also in restoring a balanced LH pulsatility and, consequently, re-establishing normal menstruation and ovulation[21-24]. Later on, many other prolactin-inhibiting agents were introduced, and it has been shown that these drugs not only regulated ovulatory and menstrual function but were also able to inhibit the growth of pituitary adenomas.

Anovulation

Disorders of anovulation account for about 30% of infertility and often present with irregular periods (oligomenorrhoea) or an absence of periods (amenorrhoea). Many of the treatments are simple and effective, so couples may need only limited contact with doctors. This makes it easier for a couple to maintain a private loving relationship than in the stressful, more technological environment of assisted conception. However, not all causes of anovulation are amenable to treatment by ovulation induction. Anovulation can sometimes be treated with medical or surgical induction, but it is the cause of the anovulation that will determine whether ovulation induction is possible[25].

Causes suitable for ovulation induction

Hypothalamic-pituitary causes

Hypogonadotropic hypogonadism is characterized by a selective failure of the pituitary gland to produce FSH and LH. The commonest cause is excessive exercise, being underweight, or both. Women who have a low body mass index (BMI), for example $<18 Kg/m^2$ or who exercise excessively, for example gymnasts, marathon runners, ballerinas, may develop amenorrhoea because of a physiological reduction in the hypothalamic production of gonadotropin releasing hormone. Women who are underweight for their height when they get pregnant are more likely to have 'small for dates' babies; and children of women who have eating disorders are more likely to be admitted to hospital with failure to thrive. Sheehan's syndrome (panhypopituitarism), caused by infarction of the anterior pituitary venous complex (usually after massive postpartum haemorrhage or trauma), and Kallman's syndrome (amenorrhoea with anosmia caused by congenital lack of hypothalamic production of gonadotropin releasing hormone) are rare. Children treated for a craniopharyngioma or some forms of leukaemia may have hypogonadotropic hypogonadism secondary to cerebral irradiation, which may affect the hypothalamus or the pituitary[25].

Hyperprolactinemia is usually caused by a pituitary microadenoma. This leads to a reduction in the production of pituitary FSH and LH. Although the commonest presentation is secondary amenorrhoea, some women may present with galactorrhoea. A smaller number may have headaches or disturbed vision that may indicate a macroadenoma, which needs urgent investigation and treatment. A microadenoma is easily treated with drugs with a subsequent resumption of menses and fertility[25].

Ovarian causes

Polycystic ovary syndrome is the commonest cause (70%) of anovulatory infertility[26-30]. The primary abnormality seems to be an excess of androgen production within the ovary[31,32] that leads to the recruitment of large numbers of small preovulatory follicles, which fail to respond to normal concentrations of follicle stimulating hormone[33]. Thus, a dominant follicle is rarely produced. Women with polycystic ovary syndrome commonly present their late teens or early 20s with hirsutism, acne, or irregular periods (cycle length > 35days). Even if they ovulate, the chance of conception for these women is reduced because fewer ovulatory events occur in a given time frame. Obesity is present in varying degrees (30% to 70%) in women with the syndrome and is usually of the central type[34-36]. Central obesity, being a prominent feature of the so-called metabolic syndrome, is directly linked to increased peripheral insulin resistance (IR)[37]. Furthermore, PCOS itself has been shown to confer a risk for insulin resistance, beyond that caused by obesity alone[38].

Causes unsuitable for ovulation induction

Premature ovarian failure (premature menopause)

Unfortunately, this is an irreversible condition. The only treatment option that can result in conception is the use of donated eggs with in vitro fertilization. Patients will need hormone replacement therapy to alleviate menopause symptoms and to reduce loss of bone density[25].

Genetic abnormalities

The commonest genetic abnormality is Turner's syndrome (45,X0), in which underdeveloped (streak) ovaries result in primary ovarian failure (premature menopause). With adequate estrogen replacement the uterus can grow large enough for the women to conceive using donated eggs with in vitro fertilization. Some translocations and deletions of the X chromosome also cause ovarian failure.

Ten per cent of primary amenorrhoea is caused by androgen insensitivity syndrome (formerly testicular feminization). These women have a 46,XY karyotype and intra-abdominal gonads that are testes but have developed as phenotypically female because of the absence of, or non-functionality of androgen receptors. The vagina usually ends blindly and, as there is no uterus, pregnancy is impossible. The gonads should be removed because of an increased risk of malignant change. Explaining the nature of the problem to the patient needs care and sensitivity, and longer term psychological support may be needed[25].

Ovulation induction

Treating specific causes

Change of weight

Women with polycystic ovary syndrome who are obese (BMI $> 30 Kg/m^2$) should be advised to lose weight[25,34]. Together with exercise weight loss (even as little as 5% of body mass) reduces insulin and free androgen levels[36], resulting in improved menstrual regularity, ovulation, and pregnancy rates. If a woman is obese when she is pregnant she is more likely to miscarry. Women who are underweight (BMI $< 18 Kg/m^2$) should be encouraged to gain weight, and no infertility

treatment should be offered until their body mass has returned to the lower limits of normal.

Hyperprolactinemia

Bromocryptine is safe and commonly used. Treatment should start with a dose of 1,25mg (taken with food) at night for the first fortnight and then increased to 2,5mg for another fortnight. The prolactin level should be checked, and if the level is below 1000 IU/L, the dose should be maintained. The side effects of bromocryptine (postural hypotension, nausea, vertigo, and headache) can make it unacceptable to the patient. Cabergoline and quinagoline are newer long acting dopamine agonists with fewer side effects. Once prolactin levels have returned to below 1000 IU/L the woman's periods should return and 70-80% of women will ovulate[25].

Hypothyroidism

In hypothyroidism thyrotropin releasing hormone (TRH) may stimulate prolactin secretion in addition to TSH from the anterior pituitary. Correction of hypothyroidism with thyroxine replacement allows thyroid stimulating hormone and prolactin levels to return to normal, releasing the suppression to gonadotropin secretion and ovulation[25].

Medical induction

Pulsatile gonadotropin releasing hormone

Treatment with gonadotropin releasing hormone that is started in a specialized hospital setting may be suitable for women who have a purely hypothalamic cause for their amenorrhoea, for example women with recovered weight related to amenorrhoea but who are still not ovulating. The woman wears a small mechanical syringe pump that can deliver a pulse of gonadotropin releasing hormone subcutaneously every 90 minutes, and this usually leads to unifollicular ovulation. Local reactions may occur at the injection site. Conception rates are similar to those of the normal population at around 20-30% per cycle and 80-90% after 12months use[25].

Antiestrogen treatment: clomiphene citrate

It is now >40 years ago that Greenblatt et al first reported a new compound, the anti-estrogen MRL-41, capable of inducing ovulation for anovulatory women[37]. Later to become as clomiphene citrate (CC) this compound has had a remarkably sustained career as the first-line treatment for women with absent or irregular ovulation due to hypothalamic-pituitary dysfunction associated with normal basal levels of endogenous estradiol (WHO II). The vast majority of these patients probably some 80% are now known to be oligo- or anovulatory due to polycystic ovary syndrome. Until the introduction of CC the only plausible treatment for these patients who wished to conceive was bilateral wedge resection of the ovaries[38-40].

Despite the use of CC in controlled ovarian stimulation, its original indication of ovulation induction for WHO group II classification of oligo- or anovulation, particularly when associated with PCOS, remains its most frequent and most successfully treated indication. The fact that CC is an orally administered, relatively cheap preparation has proved an enormous advantage over its injected and expensive competitors. However, the field is becoming replete with alternatives for the same indication and the time is ripe to re-evaluate the place of CC in our armamentarium of ovulation-inducing agents[39].

Clomiphene contains an unequal mixture of two isomers as their citrate salts, enclomiphene and zuclomophene. Zuclomiphene is much the more potent of the two for induction of ovulation, accounts for 38% of the total drug content of one tablet and has a much longer half-life than enclomiphene, being detectable in plasma one month following its administration. Rostami-Hodjegan et al[41] have suggested that wide variability in the metabolism of the zuclomiphene component contributes to variability in response to the drug.

Clomiphene citrate is capable of inducing a discharge of FSH from the anterior pituitary and this is often enough to reset the cycle of events leading to ovulation into motion. The release of even small amounts of FSH into the system will often induce ovulation and pregnancy in a proportion of eu-estrogenic anovulatory women. This is achieved indirectly, through the action of CC, a non-steroidal compound closely resembling an estrogen, in blocking hypothalamic estrogen receptors, signalling a lack of circulating estrogen to the hypothalamus and inducing a change in the pattern of pulsatile release of GnRH[38,39].

CC is given orally in a dose of 50-250mg per day for 5 days from day 2,3,4 or 5 of spontaneous or induced bleeding, starting with the lowest dose and increasing the dose in increments of 50mg/day per cycle until an ovulatory cycle is achieved. The starting day of treatment, whether on day 2 or through day 5 of the cycle, does not influence the result[42].

A compilation of published results regarding ovulation and pregnancy rates following treatment with CC reveals an ovulation rate of 73% and a pregnancy rate of 36%[39]. From a grand total of 4054 pregnancies, ´20% terminated in a spontaneous abortion and almost all the rest in a live birth. Although CC will restore ovulation in ´73% of patients, it will result in pregnancy in only ´36%. The 27% of anovulatory women with normal FSH concentrations who do not respond at all are considered to be 'CC resistant'[39].

In ability of CC to induce ovulation is more likely in patients who are obese, insulin resistant and hyperandrogenic compared with those who do respond[43]. This careful prospective study pinpointed a high free androgen index as the best predictor of non-response to CC. Although it is virtually impossible to predict who will respond to which dose of CC, if at all[44], body weight

has been found to be an impending factor. Overweight women respond less well[45] and the dose of CC needed to induce ovulation correlates with body weight[46].

It is frustrating that the restoration of ovulation by CC does not produce a much higher pregnancy rate. This discrepancy between ovulation and pregnancy rates (only 50% of those who ovulate will conceive) may be partly explained by the peripheral anti-estrogenic effects of CC at the level of the endometrium and cervical mucus or by hypersecretion of LH. While the depression of the cervical mucus, occurring in ΄15% of patients, may be overcome by performing intrauterine insemination, suppression of endometrial proliferation, unrelated to dose or duration of treatment but apparently idiosyncratic, indicates a poor prognosis for conception if the endometrial thickness on ultrasound scanning does not reach 8mm at ovulation. The prevalence of endometrial suppression is one in every 6-7 patients and, if noted in the first cycle of treatment with CC, it will almost certainly be seen in repeated cycles in the same woman[39]. There is little point in persisting after even one cycle, and a step-up to other forms of ovulation induction is recommended.

The main action of CC, indirectly stimulating GnRH secretion, not only increases the desired FSH release but also produces an undesirable increase in LH concentrations. This increase in LH, whose basal level is often already high in women with PCOS, may compromise pregnancy rates in those receiving CC[47,48]. It has been demonstrated that pre-treatment with micronized progesterone is capable of modulating LH pulsatility, reducing LH concentrations and inducing a more favourable environment for ovulation induction with CC[49]. This treatment initiated a response to CC and yielded consequent pregnancies in previous non responders to CC.

A course of six ovulatory cycles is usually sufficient to know whether pregnancy will be achieved using CC before moving on the more complex treatment as it has been reported that 71-88,5% of the pregnancies achieved with CC occur within the first three cycles of treatment [43,50,51].

Gonadotropins

Patients remaining anovulatory [CC-resistant anovulation (CRA)] and patients failing to conceive during CC treatment [CC failure to conceive (CCF)] are generally treated with exogenous gonadotropins[52]. Recently, it has become more accepted to treat CRA patients with a combination of CC and an insulin sensitizer before treatment with exogenous gonadotropins is started. Individual differences in the daily amount of FSH required to induce ongoing follicle growth and ovulation (the FSH response dose) have been suggested to be the main factor of hyper-responsiveness and severe complications during FSH ovulation induction[53]. This individual variation resulted in two different approaches in ovulation induction with gonadotropins. The 'step-up' protocol aims at slowly and prudently surpassing the FSH-threshold to reduce the chances of these complications. However, this approach might result in a prolonged treatment period and late follicular phase FSH accumulation, increasing the risk of multifollicular growth. In an attempt to overcome these problems, the 'step-down' protocol has been developed, which mimics the physiological FSH profile more closely[54]. The FSH starting dose is presumed to be the response dose; hence, dominant follicle growth is established more quickly. Thereafter, the FSH doses can be reduced slowly, resulting in the development of a single dominant follicle[54]. Frequent monitoring of the ovarian response is especially important during the step-down protocol, because the duration of FSH threshold being suppressed determines whether there will be mono- or multifollicular growth [55]. Stimulation is cancelled when multifollicular growth is apparent and more than three follicles >12mm in diameter are present.

Starting with too high an initial dose in women with a low FSH threshold is the most prominent danger in step-down ovulation induction. To determine the FSH response dose for an individual patient, a low-dose, step-up regimen has been used during the first stimulation cycle. Consecutive treatment cycles were performed according to a low-dose step-down regimen, starting 37,5 IU above the response dose in the preceding 'dose finding' cycle. This approach resulted in a cumulative ovulation rate of 82%, an ongoing pregnancy rate of 58%, a singleton live birth rate of 43% and a multiple live birth rate of 5%[56]. Hence, multiple pregnancies (twins, triplets and quadraplets) represent 9% of all pregnancies after FSH ovulation induction according to the current protocol.

A prediction model was developed for the FSH response dose during the initial dose finding treatment cycle, consisting of the following parameters: BMI, CRA, free insulin-like growth factor I (IGF I) and initial serum FSH[57]. This model was validated in a different WHO 2 ovulation induction group treated according to a low-dose step-down protocol[58]. During FSH ovulation induction, changes for multifollicular development could be predicted by initial hyperandrogenism (androstenedione and testosterone), raised luteinizing hormone and increased antral follicle count (representing polycystic ovaries).

Numerous (mostly retrospected) studies have been published regarding success and complication rates in WHO 2 anovulation induction using CC[51,59] or gonadotropins[53,54,60] in various patient groups. A prospective follow up study in which a well defined group of patients was treated according to the conventional ovulation induction algorithm of CC followed by gonadotropis[61] resulted in an overall cumulative singleton live birth rate of 71% after 24 months, a cumulative multiple live birth rate of 7%, a cumulative overall live birth rate of 76% and a median time of pregnancy of 11,7 months. Initial patient characteristics predicting chances for singleton live birth during the classic ovulation induction strategy using a multivariate

prediction model were age, insulin resistance and duration of infertility.

In vitro fertilization

Twenty-six normogonadotropic anovulatory patients who previously failed to achieve a live birth after conventional ovulation induction (CC and gonadotropins) were matched (for age, treatment period and treatment regimen) with 26 tubal infertility patients starting in vitro fertilization (IVF) treatment[62]. Cycle cancellation was related to obesity. Once oocyte retrieval was achieved, the numbers of retrieved and normally fertilized oocytes and cumulative live birth rates after three IVF cycles were comparable between the two groups. After 36 months of follow up, the overall results of the total classic infertility treatment algorithm for anovulatory infertility (CC-FSH-IVF) are a cumulative pregnancy rate of 83%, a live birth rate of 80% and a singleton live birth rate of 77%[40].

Although in most European centers the majority of WHO 2 patients are still treated according to the above-mentioned conventional algorithm (CC-FSH-IVF), it might be worthwhile considering that certain subgroups could benefit from an alternative treatment strategy. For example, the FSH induction of ovulation could be omitted in some patients[63]. These patients could be offered insulin sensitizers after failure of CC treatment or, alternatively, offered IVF directly.

In a group of obese CRA/CCF patients, a cost-effectiveness comparison of different treatment regimens was performed in a small randomized controlled trial[64]. Pituitary downregulation was achieved by the administration of a gonadotropin-releasing hormone agonist in the FSH ovulation induction group, and by administration of estradiol combined with progesterone in the IVF group. Patients presenting with multifollicular development during ovulation induction were converted to 'escape' IVF treatment. It was concluded that costs per term pregnancy were higher for FSH ovulation induction. A more extensive study[63] divided 240 WHO 2 patients into several subgroups according to presence or absence of the following risk factors: age>30 years, amenorrhoea, raised androgens and obesity. For each subgroup chances for response and treatment costs were calculated based on published prediction models[44,56,61,62] and compared with prospectively collected data from the patient group. The outcome measure was ongoing pregnancy within 12 months. The conventional CC-FSH-IVF algorithm was proved to be the optimal treatment strategy for most patients. However, in hyperandrogenemic women over 30 years of age, no substantial benefit of FSH ovulation induction could be identified. Within the margins of this defined treatment algorithm, patients in this subgroup should have been offered IVF directly after CC treatment failure.

Alternative treatment options

Insulin sensitizers

The presumed central role of insulin resistance in hyperandrogenism in PCOS[65] is the reason that insulin sensitizers were introduced in ovulation induction[66]. Lowering insulin resistance might reduce ovarian dysfunction and improve ovarian responsiveness to FSH[67]. This effect might be more evident in overweight and insulin-resistant PCOS patients[67], although conflicting results have been reported. Clinically, metformin has been shown to be effective as an adjuvant of CC in CRA patients[65]. The efficacy of metformin as first-line ovulation induction is still uncertain, as is its additional role as pretreatment or co-treatment in FSH ovulation induction. Only small studies have been performed, and this indicates that metformin co-treatment could improve ovarian response during FSH ovulation induction in anovulatory infertility patients[67-69]. It is suggested that metformin co-treatment in gonadotropin induction of ovulation reduces the amount of FSH needed, significantly shortens the stimulation period and produces more monofollicular cycles.

Aromatase inhibitors

Aromatase inhibitors are a new group of drugs to join the arsenal of fertility treatments. They are orally administered, easy to use, and relatively inexpensive, with minor side effects. Anastrazole and letrozole are third-generation aromatase inhibitors that have been used for ovulatory disorders and for superovulation. To date, letrozole has been studied much more extensively than anastrazole. The data on letrozole suggests that it can be used to replace CC as the first-line treatment for women with ovulatory disorders. Compared with CC, its use is associated with thicker endometrium[70-72]. For superovulation, there is a trend for higher pregnancy rates with letrozole than with CC. When letrozole is added to gonadotropin regimens, it leads to less gonadotropin requirement and a pregnancy rate that is comparable to that with gonadotropin treatment. The role of aromatase inhibitors in assisted reproductive technologies remains to be seen. The ideal dose of letrozole is unknown; however, it seems that the dose of 5mg daily for five days is the most effective. Aromatase inhibitors are promising new drugs for the induction of ovulation and superovulation. After four decades of CC treatment, a new era of ovulation induction has finally arrived[73].

Laparoscopic electrocoagulation of the ovaries (LEO)

Bilateral electrocoagulation of the ovarian surface is performed by laparoscopy. This induces endocrine changes[74] and restoration of ovulation in most patients for one or more menstrual cycle[75]. Similar pregnancy rates have been reported during the first year after laparoscopic electrocoagulation of the ovaries compared with gonadotropic ovulation induction[75]. A large prospective randomized trial[76] reported comparative pregnancy rates after one year, with reduced multiple pregnancy rates in the LEO group. However, ovulatory cycles after LEO alone were achieved in less than 50%

of patients. The LEO group received CC and/or gonadotropins after six months. Time to pregnancy in the LEO was doubled. However, intervention does not render ovaries more susceptible to stimulation by CC[74]. One multiple pregnancy was reported in the LEO group (2%) versus nine (16%) in the CC/FSH ovulation induction group. Cost-effectiveness was increased as a result of a reduced number of multiple pregnancies in the LEO group. Patient characteristics reported to predict chances for ovulation and pregnancy after LEO in a WHO 2 infertility population, failing to ovulate or conceive after CC treatment, were hyperandrogenism (testosterone and free androgen index) and BMI, whereas raised LH serum levels increased chances for pregnancy[77]. These data could not be confirmed by a smaller prospective study in a group of patients with CRA[78]. Only age at menarche and LH:FSH ratio were significantly related to treatment response. A prospective, randomized, placebo-controlled trial comparing metformin to LEO in overweight, infertile, CC-resistant women with PCOS concluded that metformin administration was more effective in overall reproductive outcome and in health[79]. Long term effects and perioperative morbidity were not evaluated.

Conclusion and future perspectives

Although evidence-based medicine has been practised in reproductive medicine for a long period of time, large multicenter, randomized controlled trials[76,65,80] are rare in the field of ovulation induction. Hence, single-centre, randomized or longitudinal follow up studies are often used to obtain more insight into the optimal treatment of individual patients. There is a tendency to shift first-line treatment of anovulatory infertility patients from ovulation induction towards assisted conception (IUI and ovarian hyperstimulation, followed by IVF with or without in vitro oocyte maturation), bypassing classic ovulation induction[38].

One major step towards a better understanding of features predicting success or complications after ovulation induction in the notoriously heterogeneous WHO 2 group is the paradigm shift from diagnosis (focusing on aetiology) to prognosis of treatment outcome. This shift in emphasis coincides with the first global consensus on criteria for PCOS diagnosis[81,82]. The criteria for PCOS diagnosis used in the new consensus also predict chances for success and complications during ovulation induction. The chance to a uniform definition enables all researchers to combine their strength and reduce the WHO 2 treatment strategy dilemma.

Nowadays, awareness is growing that patient characteristics rather than treatment modalities determine both treatment complications and outcome. This implies that eventually we will need to abandon the current paradigm that one compound or dose regimen is the most suitable treatment strategy for all patients, and chance to a more individually tailored approach, based on patient characteristics assessed by initial screening[83]. As suggested by several studies, this approach will improve safety, efficiency and health economics of anovulation treatment. It might also enhance our understanding of processes involved in anovulatory infertility. The overall chances of treatment success and complication rates can be calculated and discussed with the patient before treatment is initiated.

The most important predictors for treatment outcome were age, BMI, hyperandrogenism and insulin resistance[44,56,61,62]. However, these predictors are only applicable to the study population and can only be clinically applied after validation in different patient populations.

Although results with the conventional ovulation induction protocol might be acceptable, with a cumulative singleton live birth rate as high as 71% before IVF is started[61], it is possible to induce new modalities in the classic treatment algorithm, such as insulin sensitizers, aromatase inhibitors or laparoscopic electrocoagulation of ovaries, which might improve the outcome even further. Moreover, the cost-effectiveness of various individualized treatment protocols should also be taken into account, and might further optimize individualized ovulation induction treatment algorithm[40].

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