UCLouvain

Faculté de médecine et médecine dentaire

Individualizing gonadotropin dose in IVF treatment: the role of AMH and BMI in prediction models

Auteure : Jessica Jordanova
Promotrice : Pr. Christine Wyns
Lectrices : Pr. Céline Pirard, Pr. Orsalia Alexopoulou
Année académique 2019-2020
Master en Médecine, à finalité spécialisée

Table of contents

Acknowledgements

I would like to express my deep gratitude to my Promoter Professeure Christine Wyns, who has, since the onset of this project, devoted herself in guiding me to explore her area of expertise and has generously shared her knowledge.
This work would not have been possible without her leadership and dedication to my progress. I hope to expand on this experience in the future to further my knowledge under her invaluable guidance.

I also wish to thank Ms. Patricia Van Aken for her endless cooperation and support. Working closely together on an ongoing basis, she became a source of encouragement and was everpresent to answer my countless questions.

I would also like to extend my gratitude to Professeure Céline Pirard for her generous advice and guidance throughout this research project.

My recognition goes out to Professeure Annie Robert, for her continuous statistical advice and teaching in the completion of this work.

To my family and friends, I give my heartfelt thanks for their unwavering reassurance and belief in my work. It provided me with the much needed self-confidence and perseverance to realize this project.

Finally, I am indebted to all members of this jury for their dedication and unquestionable support. It is with great humility and gratitude that I thank you.

Individualizing gonadotropin dose in IVF treatment: the role of AMH and BMI in prediction models

Abstract

Objective

Previous studies concerning individualized versus standard IVF treatment protocols show controversial results.

The objective of this study is to apply a new drug dosing algorithm for ovarian stimulation based on anti-müllerian hormone serum concentration, small antral follicle count (2-5mm) and body mass index to a population of women undergoing IVF/ICSI treatments. The algorithm would help us to determine if there is a benefit in terms of the number of oocytes retrieved as the primary endpoint compared to a standard protocol of ovarian stimulation.

Secondary outcomes include recombinant FSH dose, dose adjustment rate, duration of stimulation, ovarian hyperstimulation syndrome (OHSS), clinical pregnancies and live birth rate per transfer.

Methods

In this prospective multicenter trial patient recruitment started in September 2016, and so far 150 patients have been randomized including women aged 18 - 43 years undergoing a GnRH antagonist IVF/ICSI treatment protocol. Women were assigned to the study group where human recombinant FSH was administered using the dosing algorithm for the starting dose or the control group where recombinant FSH was given at a dose as currently applied in the ART center. Gonadotropin dose adjustment was allowed as of day six in case of insufficient or excessive ovarian response.

Results

A halfway study analysis showed that the primary outcome, total percentage of patients with recovered mature oocytes (5-15) were similar between study (57.5%) and control group (56.3%) ($p = 0.88$). Dose increase after day 6 was significantly higher in study group ($p = 0.04$). The dose was increased in 43% of patients receiving <=150 IU/day in study group and 14% in controls ($p = 0.01$), even though total duration of stimulation as well as total dose of FSH consumed were similar between groups. In patients receiving > 150-< 300 IU/day and >= 300 IU/day, no difference was observed in the proportion of patients with a dose adjustment between groups. No cases of severe OHSS were observed in this trial. Live birth rate per transfer was 18.2% and 28.1% in study and control group, respectively (p = 0.18).

Limitation

Currently, less than half of the number needed to treat has been included in the trial; which is insufficient for proper statistical analysis and interpretation. It is indisputable that other questions will arise once total study population will be analysed.

Conclusion

To this day, there is no evidence of a superiority with regard to efficacy and safety in an individualized protocol based on an algorithm compared with a dose as applied without algorithm based on current practice in an ART center.

Keywords: IVF - ICSI - Dosing algorithm - Anti-Müllerian Hormone - Body Mass Index - antral follicle count - ovarian stimulation - individualized treatment

Individualisation des traitements de stimulation ovarienne en FIV : rôle de l'AMH et du BMI dans les modèles de prédiction

Résumé

Objectifs

La littérature scientifique ne présente pas à ce jour un consensus clair quant au bénéfice d'une approche individualisée versus une approche standard de stimulation ovarienne en vue d'une Fécondation In Vitro.

L'objectif de cette étude est de tester sur une population de femme entamant une FIV/ICSI un nouvel algorithme de stimulation ovarienne individualisé basé sur l'hormone antimüllérienne, le compte des petits follicules antraux (2-5mm) ainsi que l'Indice de Masse Corporelle. L'hypothèse principale recherchée par cet algorithme est l'amélioration de la proportion de bonnes répondeuses, étant définie comme l'obtention de 5 à 15 ovocytes matures après stimulation ovarienne par gonadotrophines.

Les outcomes secondaires incluent la dose d'attaque de FSH recombinante, l'ajustement des doses, la durée totale de stimulation, le taux de syndrome d'hyperstimulation, le taux de grossesse cliniques et le taux de naissances par transfert d'embryon.

Méthodes

Cette étude prospective multicentrique a commencé le recrutement de patientes en septembre 2016 et à ce jour, 150 patientes ont été randomisées. La population de femmes étudiées avait entre 18 et 43 ans et était éligible pour un protocole de type antagoniste de la GnRH. Le groupe étude a reçu l'administration d'une dose de FSH recombinante calculée sur base de l'algorithme ; tandis que le groupe contrôle a reçu une dose correspondante à celle habituellement administrée dans le service. La modification de la dose initiale attribuée de FSH était autorisée à partir du sixième jour dans le cas d'une stimulation ovarienne insuffisante ou excessive.

Résultats

L'analyse à mi-chemin montre une proportion de bonnes répondeuses évaluée par un nombre totale d'ovocytes matures (5-15) similaire entre les deux groupes (57.5% dans le groupe étude et 56.3% dans le groupe contrôle ; p = 0.88). La proportion de patientes pour lesquelles la dose avait été majorée au 6ème jour était significativement plus élevée dans le groupe étude (p = 0.04). Une augmentation de FSH était observée chez 43% des patientes dans le groupe étude recevant <=150 UI/jour et 14% dans le groupe contrôle (p = 0.01), bien que la durée de stimulation ainsi que la quantité totale de FSH consommée étaient similaires. Dans les autres catégories de doses administrées (>150-< 300 UI/jour et >= 300 UI/jour), aucunes différences n'ont été observées quant à la proportion de femmes avec un ajustement de dose au sixième jour. Il n'y a pas eu de cas sévères d'hyperstimulation ovarienne. Le taux de naissances par transfert était respectivement de 18.2% et 28.1% dans le groupe étude et contrôle (p = 0.18).

Limites de l'étude

A ce jour moins de la moitié des patientes ont été incluses dans l'étude et le nombre nécessaire pour une évaluation robuste et interprétation des données n'est donc pas encore atteint. Il est indéniable que de multiples autres questions émergeront lors des analyses futures.

Conclusion

Actuellement, nous n'avons pas démontré une supériorité quant à l'efficacité et la sécurité d'un régime individualisé sur base de l'algorithme comparé à une pratique standard sans cet algorithme.

Mots clés : FIV – ICSI – Algorithme – Hormone antimüllérienne – Index de masse corporelle – compte folliculaire antral – stimulation ovarienne – individualisation

Introduction

Infertility, a worldwide health issue, is defined by the World Health Organization (WHO) as the inability for a couple to conceive after a year of unprotected sexual intercourse and is a common issue concerning 15% of reproductive-aged couples. Approximately one third of cases originate from the woman, another third originate from the man and the last third is a direct result of their association ("ART fact sheet, 2014"; ESHRE). Some couples can be treated directly by an appropriate hormonal therapy, or an artificial insemination. In other cases, such as the absence of both fallopian tubes or severe sperm abnormality, couples may directly be eligible for In Vitro Fertilization (IVF). This method works to ultimately fuse the male and female egg artificially in vitro in a test tube after egg retrieval during a natural or FSH stimulated cycle. It was in 1978 that the first IVF treatment was successful, leading to a healthy baby girl; Louise Brown. Since then, infertility treatment has been in constant evolution, with extremely promising outcomes.

A woman's natural menstrual cycle is dependent on a complex variation of hormonal concentrations. The cycle starts with menstruations on day one. As estrogen and progesterone decrease in the luteal phase of the menstrual cycle, follicle stimulating hormone (FSH) secretion is no longer inhibited and thus can start follicle recruitment and maturation (at day one of cycle). FSH peaks at day 3 and decreases with follicular growth due to the production of inhibin B by granulosa cells as well as a negative feedback by increasing levels of estrogen concentration. Only the most FSH-sensitive follicle will be selected to continue the maturation phase, leading to ovulation on day 14. To increase the efficiency of follicle recruitment and maturation compared to the natural cycle, ovarian stimulation to achieve the growth of several follicles at once is usually performed during IVF/ICSI treatments.

Generally, an IVF treatment includes three steps. The first phase aims to stimulate the growth of several follicles in the ovaries through injection of human urinary or recombinant FSH. In IVF, the amount of FSH to achieve an optimal number of follicles can vary between patients and is typically determined taking into account the women's age, basal serum FSH on cycle day 3, the antral follicle count (AFC), serum AMH regardless of the moment or presence of a cycle, the presence or not of polycystic ovaries (PCO) and previous response(s) to stimulation treatments. Regardless, this standard dosing regimen does not adequately optimize the number of oocytes retrieved, because of the inter variability in ovarian response to stimulation, ending up at times with some unexpected results and implications on the efficacy and safety of treatment.

Subsequently, induction of the final maturation of the follicle by either injection of hCG or a GnRH agonist is needed in order to get the oocyte ready for ovulation. Finally, the third phase consists of preparing the uterus for the implantation of the embryo, by means of a progestogen; or in case of a GnRH ovulation triggering by using low dose hCG and/or intensive estrogen and progesterone supplementation.

In the current study, we will focus on the initial phase, seeking to reach an optimal number of retrievable oocytes.

As underlined above, when starting IVF/ICSI treatment, it is important for a physician to consider including certain predictive factors whilst deciding a patients' treatment protocol, to not only determine the best success rate; which is the significative finality for the couple; but also, to adjust hormonal therapies based on a patient's individual characteristics. Besides obvious factors such as age, infertility cause, previous pregnancies, lifestyle habits, more subtle factors such as BMI and ovarian reserve markers should be taken into account. The latter will subsequently be discussed in more dept throughout this work.

Reaching the optimal number of retrievable oocytes is a key component to IVF success rates per initiated cycle and for patient safety. Indeed, a lower stimulation, hence a poorer yield of oocytes might compromise treatment prognosis, whereas hyperstimulation can put the patient at risk of Ovarian hyperstimulation syndrome (OHSS). OHSS is a severe iatrogenic complication of hormonal therapy in IVF, characterized by a fluid shift from intravascular to the third space, due to an increase of capillary permeability (Kumar P. et al., 2011). In consequence, personal evaluation of the risk-benefit balance should not be underestimated when deciding on a treatment protocol.

Three important components influencing the ovarian response in IVF treatment will be our main focus: Body Mass Index (BMI), antral follicle count (AFC) and Anti-Mullerian Hormone (AMH).

The prevalence of overweight and obese women has become a global epidemic, impacting many systems in the human body, including reproductive health.

In a natural cycle an obese woman (BMI greater than 30 kg/m²) will tend to have greater anovulation, uterine bleedings, an increased miscarriage rate and pregnancy complications (Boots, et al. 2011; Rich-Edwards et al. 2002). The outcome of obese women in Assisted Reproduction Technologies (ART) was evaluated in a metanalysis performed in 2007 clearly stating that overweight women were less likely to get pregnant by IVF treatment, that lower number of oocytes were retrieved despite a gonadotropin dose increase and that their miscarriage rate was higher. (A. Maheshwari et al. 2007)

It can be quite hard to parse out the exact physiological relationship between obesity and infertility in patients because it is multifactorial. Factors such as adipokine dysregulation, insulin resistance, dysfunction of the hypothalamic-pituitary-gonadal axis necessary in the regulation of feminine hormones and binding proteins (SHBG), hyperandrogenemia, PCOS, inflammation and many more, are part of this complex mechanism. It has been demonstrated that even a small weight loss amongst overweight and obese women improves fertility (Clark et al., 1998) by improving ovulation rate.

It is also well demonstrated that most of a drug's absorption is dependent on BMI, and henceforth a greater dosage is required to have the same effect due to a larger distribution volume in overweight and obese patients. This applies to FSH administration (Wittermer et al., 2000), and should therefore be considered to avoid inappropriate response to stimulation. Supporting the latter, Christensen et al., 2016, conducted a study to investigate if the number of previous attempts of IVF treatment cycle modified the quantity of retrieved oocytes in a series of four BMI groups. This study concluded that the median number of oocytes did not differ in four BMI groups all cycles combined, but that due to insufficient response in the first cycle, the overweight and obese group had fewer oocytes retrieved. By increasing their FSH dose in the following cycles, optimal oocyte quantity could however be reached. Consequently, we consider BMI to be an important determinant of a dose adjusting algorithm.

The International Glossary on Infertility and Fertility Care, 2017 defines ovarian reserve as "a woman's number and/or quality of oocytes, reflecting her ability to reproduce" (Zegers-Hochschild, 2017). A large number of studies have been conducted comparing different markers used over time to determine the ovarian reserve, such as age, AFC, basal FSH at cycle day 3 and AMH.

AMH is a glycoprotein hormone which plays a critical role in sex differentiation during fetal growth preventing the development of Müllerian ducts in boys. AMH is also secreted during folliculogenesis as a product of granulosa cells mainly from small pre-antral phases, making AMH a cycle independent biomarker of a woman's ovarian follicular reserve (Tan et al., 2011, Nelson et al. 2019).

A growing amount of studies have recently demonstrated that AMH is the preferred marker to predict the number of follicles that will grow following FSH stimulation (Nelson et al., 2007), but that the AFC is also a good predictor (Broer et al., 2013; La Marca et al., 2010) and that their combination is best at predicting both expected low and excessive responders. However, AFC has a higher inter-observer variability due to variation in ultrasound equipment and skills (Nelson et al. 2015). As to AMH, significant disparity between assays is observed and therefore has an impact on dosing algorithms when calculating FSH starting doses (Bungum et al. 2018). Hence, in order to avoid a potential bias in starting FSH dose in an individualized protocol, it is of great importance to consider using the same assay throughout a trial.

AMH is an appropriate predictor for both low and high responders to stimulation (although better for high response) (Hamdine et al., 2014); hence, high AMH levels were associated with lower cancelation rates, the retrieval of more eggs and a higher cumulative live birth rate (Chaitanya et al., 2017; Gomez et al., 2015; Nelson et al., 2007). Supporting the previous statement that a higher oocyte yield leads to an increase in cumulative live birth rate (CLBR), Drakopolous et al., (2016) showed that CLBR can increase up to five times with increased oocyte yields.

To summarize, AMH appears to be a superior marker for ovarian reserve, is better at predicting ovarian response and is considered as a more stable biomarker independent of physicians' bias and should therefore be a main focus in studies on individualization of therapies.

The evolving field of individualized medicine has taken a leap the last few years especially with regard to reproductive health. Even though much about its applications and benefits remain unclear, the question arises as to whether there is a benefit for personalized controlled ovarian stimulation (COS) over standardized COS? As variations in women's ovarian response during stimulation are reported, personalized drug therapies aim to anticipate these differences, optimizing the woman's chances of getting pregnant and increasing safety of the patient by avoiding OHSS.

The International Federation of Fertility Societies (IFFS) performed a survey to determine practitioners' opinions on which parameters are most likely to influence COS outcome. Age was the most popular response, followed by PCOS, AFC, AMH dosage and FSH basal level. In present day practice physicians tend to automatically individualize treatment based on many parameters through a profound anamnesis, physical examination and additional medical tests. Hence the question arises if a dosing algorithm can surpass the broad knowledge of an experimented specialist?

Reaching an optimal number of oocytes represents a critical challenge when undergoing ovarian stimulation in an IVF/ICSI treatment. Although this optimal oocyte number has been under debate, it seems reasonable to define a conventional ovarian response to stimulation as the pick-up of 6-15 oocytes (Ji et al., 2013), whereas an oocyte number over 16 increases the risk of OHSS. (Steward et al., 2014). Furthermore, "the two most important predictors of the fresh and cumulative live birth rate are quantity and quality of embryos" (Cai et al., 2011). In addition, cumulative live birth rate seems to increase parallel to oocyte yield, up to three and a half times when retrieving between ten to fifteen oocytes (Ji et al. 2013; Drakopoulos et al. 2016).

A current challenge for reproductive specialists lies in patients with poor ovarian response (POR). The first attempt at standardizing the definition of POR arose in 2011 "The Bologna Criteria" with three parameters included (age >= 40 years; previous POR and a low ovarian reserve test AFC <5 or AMH < 0.5 ng/mL) (Ferraretti AP et al. 2011). More recently in 2016, "The Poseidon criteria" was developed aiming to identify in addition to a POR population, an evidence-based therapeutic handling of such patients (Humaidan et al, 2016). An increasing proportion of women tend to postpone motherhood to their late thirties – early forties, motivated by professional and socioeconomic reasons, resulting in a growing number of older patients referred to ART treatments. Hence, the major explanation to POR is the decrease in recruitable follicles, typically the loss of follicle FSH receptors and thereby their ability to grow. However, POR can additionally occur in women with suboptimal exogenous FSH dose during stimulation independently from their ovarian reserve. Consequently, in this study we aim to integrate these findings in order to try to ameliorate outcomes in this population of women receiving a suboptimal FSH starting dose.

A number of studies have attempted to elaborate FSH dose algorithms seeking a balance between a maximal success in treatment with a minimal hyperstimulation risk. The first randomized clinical trial to compare an individualized dose to a standard dose of recombinant FSH in patients undergoing IVF was published by Popovic-Todorovic et al., in 2003. The individualized dose was based on age, smoking history, total ovarian volume, total ovarian doppler score and AFC (<10mm). According to these parameters an FSH nomogram was developed with administered doses of 100 to 250 IU of FSH for 7 days in the study group. The control group was administered 150 IU of FSH for 7 days. The results showed that the optimal number of oocytes (defined as 5-14) was retrieved in 77.1% of patients in the study group, versus 65.6% in the control group ($P < 0.05$). Poor ovarian responses were significantly lower in the study group (1,5% vs 10,7%; $P < 0.05$), whereas there was no group dependence for high responders. In addition, 86% of study patients did not require a dose modification on day 8 versus 45% of patients in the control group. Lastly, a higher rate of ongoing pregnancies was reported in the individualized protocol (36,6% vs 24,4%; P < 0.01).

A few years later the CONSORT paper was published (Olivennes et al. 2009) reporting a prospective uncontrolled study, which tested an algorithm that calculated a starting FSH dose with 37.5 IU increments based on four factors: basal FSH, BMI, age and AFC (<11mm) (Howles et al., 2006). The minimum dose of FSH was set at 75 IU, which might explain the higher cancellation rate for insufficient ovarian response in contrast to the previous study where the minimum starting dose was set at 100 IU (Popovic-Todorovic et al., 2003). The total FSH consumption decreased using the CONSORT calculator and the rate of OHSS (6.3% vs 12.5%) was cut by half. It is therefore not surprising to observe that only 83,9% of patients reached oocyte retrieval, mainly related to the increased cycle cancellation due to lower FSH starting doses. Hence, even though low doses as 75 IU/day may be suitable for a number of patients, further studies are essential to predict which patients would not respond adequately to such low doses of FSH.

The next team of physicians who created a prediction model for the FSH starting dose was La Marca et al., in 2012, who developed a nomogram based on 3 parameters: age, AMH and day 3 FSH. This nomogram was tested out in a prospective controlled study (Allegra et al., 2017) with, as the primary outcome studied being the number of retrieved oocytes. In the control group, the FSH starting dose was set according to age: participants < 35 years were administered 150 IU whereas participants > 35 were administered 225 IU. An optimal response (set at 8-14 oocytes) was observed in 63% of women included in the study group and 42% in the control group ($p < 0.05$). These results clearly demonstrate that age alone is an inadequate prediction factor and should not be used independently when deciding on an FSH starting dose.

In another attempt of individualization of IVF treatments, the ESTHER-1 (Evidence Based Stimulation Trial with Human rFSH in Europe and Rest of the world) randomized multicenter non-inferiority phase 3 trial conducted by the pharmaceutical firm Ferring evaluated the efficacy and safety of a new recombinant human FSH or Follitropin Delta which included an algorithm based on patients BMI and AMH to individualize the dose of Follitropin delta to be administered daily without adjustments during stimulation. The control group used the standard 150 IU of follitropin alfa with possible dose adjustments when needed. A total of 1,329 women aged 18 to 40 years were included. The main outcomes measured were ongoing pregnancy and implantation rates with a non-inferiority margin of 8% which is the greatest clinically approved difference required to be observed between the new drug and the standard drug in order for the new drug to be proved effective. While the results were not significantly different, proving the non-inferiority of FSH delta, the individualized group resulted in a larger proportion of women that reached their goal oocyte number (8 to 14) with less poor and high responders, as well as a lower rate of severe OHSS. Hence, following these conclusions the test drug being the first rFSH to be administered with an individualized dosing pattern dependent on patients' AMH and BMI, has been granted by the European Commission marketing authorization in December 2016 and has been approved in 37 countries.

In contrast, the possibility to increase the live birth rate which is undoubtedly considered to be the outcome parameter which matters most to patients remains to be demonstrated as in the majority of studies on individualized IVF treatments no significant improvement over conventional treatment was shown. Hence, live birth being the most important finality to couples, physicians tend to presently consider this outcome measure as a primary end-point in more specific populations of women.

Published in 2017, the OPTIMIST study was a Dutch randomized controlled trial comparing an individualized versus a standard intervention. It included a total of 1042 women on their first round of IVF treatment between 2011 and 2014. Two categories of patients were studied according to the predicted ovarian response based only on the AFC. Firstly, poor responders (n = 511) were selected based on a total number of follicles sized below or equal to 10mm (Van Tilborg et al., 2017). This subpopulation was further divided into a standard 150 IU/day group and an individualized group administering 450 IU/day to women with AFC ≤ 7, and 225 IU/day to those with AFC between 8 and 10. The second subpopulation consisted of excessive responders (n = 531) with an AFC exceeding 15 (Oudshoorn et al., 2017). This patients' group was randomized into individualized 100 IU/day group or standard 150 IU/day group. The primary outcome for all patient populations was an ongoing pregnancy resulting in live birth within 18 months following randomization (Oudshoorn et al., 2017, Van Tilborg et al., 2017). Several secondary outcomes were considered such as clinical pregnancies, excessive response, cycle cancellation and number of retrieved oocytes.

The result of the study showed no significant rise in the cumulative live birth rate for individualized regimens. Despite this, increasing doses in predicted poor responders resulted in a higher oocyte yield, higher embryo transfer rate and a lower rate of cycle cancellation. In predicted hyper responders, severe OHSS was not different in individualized group, but the total proportion of women who suffered from mild OHSS diminished (5.2% vs 11.8%). Cost-effectiveness was also evaluated in both studies and the authors concluded that a dose reduction in hyper responders was not altogether less expensive, whereas in women where a higher dose of FSH was administered, treatment cost was increased. The study was criticized due to an inappropriate definition of the term ‘poor responder’. Indeed, the patients included in the expected poor responders did not comply with the established either Bologna or Poseidon criteria. Another major criticism was the use of doses as high as 450 IU/day, considering doses above 300 IU/day showed to not add any benefit with regard to ovarian response and increase cost of treatment (Berkkanoglu et al. 2010). Finally, a major limitation in this study was the performance of AFC and AMH blood sampling after ovarian downregulation which might have influenced patient classification in predicted response groups.

Most recently, an AMH-based individualizing algorithm was assessed on a population of women undergoing a first IVF/ICSI cycle by means of a GnRH antagonist protocol with as a primary outcome optimal oocyte retrieval set at 4-15 oocytes (Petersen et al. 2019). Secondary outcomes included excessive response (>15 oocytes picked up), OHSS, ongoing pregnancy and LBR. The algorithm assigned 100 IU/day of rFSH when AMH > 24pmol/L; 150 IU/day of rFSH for AMH= 12-24 pmol/L and when AMH < 12pmol/L corifollitropin 100 to 150µg depending on body weight (+/-60kg). Neither any increase in the proportion of women who reached the optimal oocyte yield was observed nor any difference in live birth rate were observed. Clearly, 100 IU/day was insufficient and led to a significantly increased proportion of patients with low response (< 5 oocytes retrieved). A major limitation recorded in this trial was the switch of AMH assay at midpoint through the patients’ recruitment.

Clearly, there is so far insufficient evidence to close the debate on individualizing or standardizing ovarian stimulation in IVF/ICSI treatments. Nevertheless, it is clear that one size does not ‘fit all’, and that an individualized protocol is superior to a standard regimen of 150 IU/day for all patients. Dosing algorithms show evidence as to an increased patient safety, an overall better prediction in oocyte yield with ovarian reserve markers and a decrease in risk of cycle cancellation. It may be assumed that alternative algorithms or adjustments in algorithm including different parameters could help to reach better outcomes.

It is therefore by means of a new dosing algorithm, that we aim to analyze in this study the role of combining several individualizing parameters (AMH, BMI and AFC) in prediction models.

Materials and Methods

Design

This study is a prospective multicenter randomized controlled clinical trial. The study has been approved by the Ethics Committee of Cliniques Universitaires Saint-Luc in Brussels (CUSL); registration number B403201524419 and is registered in clinicaltrials.gov.com.

Patient Population

Twenty-six women were randomized in study center in Beirut and 124 women in CUSL. The study included patients eligible for an IVF/ICSI GnRH antagonist protocol treatment. Patients were aged between 18 and 43 years with a BMI < 40 kg/m² voluntarily accepting to participate in the research. Patients needed to have normal blood levels of thyroid stimulating hormone (TSH) and prolactin within the 6 months prior to the start of treatment. Within the same period, dosage of basal FSH, LH and estradiol were indispensable. AMH serum concentration was also requested within 2 months prior to preparation with oestro-progestative contraceptive pill. Patients were excluded from the trial for the following reasons: PCOS, unresolved thyroid problems, non-treated hydrosalpinx, a history of more than three consecutive miscarriages, hypogonadotropic hypogonadism, unresolved hyperprolactinemia, a known hyper sensibility to study medications, a history of OHSS, a single ovary, congenital malformation of the reproductive tract, genetic abnormalities and morbid obesity (>40 kg/m²).

Patients must have given written informed consent and were allowed to withdraw from the study at any time with no explanation required. Likewise, if the patient did not follow treatment instructions, the doctor could remove her from the study.

Algorithm

The goal behind this study was to test a new algorithm’s ability to predict ovarian response, seeking an optimal starting dose of rFSH to administer to the patient, based on individual characteristics. The algorithm included three prediction factors: AMH, BMI and AFC (2-5mm). Women were randomized into an individualized treatment group (study group) who received the algorithmically calculated dose of rFSH, versus an empirical rFSH dose (control group). In the control group, the doses of rFSH were administered following the current applicable method in the department (based on age, AFC, basal FSH, results of previous ovarian stimulation and doctors’ experience). In the study group, for each preantral follicle

measuring 2 to 5mm, 20 IU of rFSH was administered. This dose was based on pharmacokinetic studies, which established that the maximal endogenous dose of FSH required for a monofollicular recruitment in a natural cycle is 14-16 mIU/mL (Owen J. Jr. 1975 and Hadlow N. 2013), and on pharmacodynamic studies where rFSH was shown to have a 75% absorption rate. The AMH value used in the algorithm was obtained randomly throughout menstrual cycle and measured using a Beckman Coulter immunoassay analyzer. Height and weight were used to calculate the BMI according to the following formula: BMI = kg/m^2.
A correction factor for AMH and BMI (Nelson S. 2013; Fleming R. 2013) was applied in order to calculate the daily rFSH dose for the first 5 days of stimulation as follows:

AMH pmol/L	Predicted ovarian response	Correction factor
< 1	extremely low	x4
1 - 6	low	x2
7 - 18	normal	none
>18	high	x0.5

BMI (kg/m2)	Body type	Correction factor
16.5 – 18.5	thinness	x 0.75
18.5 - 25	normal	none
25 - 30	overweight	x 1.25
30 - 35	moderate obesity	x 1.5
35 - 40	severe obesity	x 2

Formula:

Daily starting rFSH dose: 20 IU x AMH correction factor x BMI correction factor x number of follicles (2-5 mm) at day 3

Interventions

The AFC was determined on day 3 of a cycle within 2 months prior to the start of treatment by the means of a transvaginal ultrasound (US). AMH is expressed in the granulosa cells of preantral and small antral follicles measuring < 6mm, and this expression tends to cease with the growing towards dominant follicles (Weenen et al., 2004). Therefore, in the present study we distinguished follicles measuring 2-5mm from those 6-10mm, and hence exclusively the number of follicles measuring 2-5 mm were included in the algorithm.

All patients entered an antagonist protocol. The treatment protocol began on day 1 (five days after the end of oral contraception) with daily injections of rFSH (Gonal-F®), after having taken an oral contraception for at least two weeks.

The dose was to be maintained for 5 days. On day 6 of stimulation ovarian response was assessed by vaginal US, after which dose adaptation was allowed in case of insufficient ovarian stimulation and on the opposite if there was a risk of developing an excessive response. Dose adjustment was considered significative when ≥ 50 IU variation.

The US was concomitant with blood sampling, and this every second-third day beginning on day 6. Blood sampling included estradiol, FSH, LH and Inhibin B levels, and with addition of progesterone on the day hCG was administered.

A daily dose of 0,25 mg of GnRH antagonist (Cetrotide®) was started once at least one follicle had reached 13-14mm. Final oocyte maturation by hCG (10 000 UI Pregnyl® or 5 000 UI Pregnyl® or 250 µg Ovitrelle® (corresponding to 6500 UI rHCG)) or a GnRH agonist in the case of OHSS risk (0.2mg Decapeptyl®) was administered when at least 3 follicles had reached 17mm.

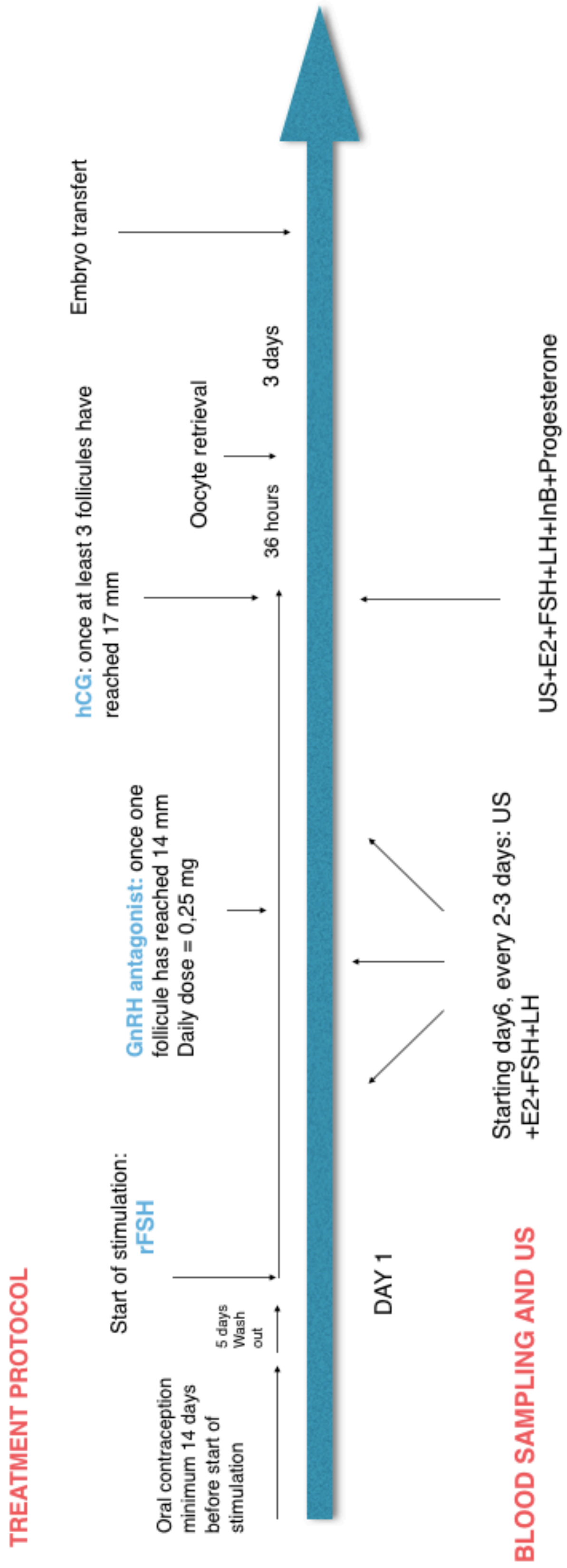
Oocyte aspiration was performed transvaginally 36 hours after hCG injection. Luteal phase was supported by vaginal progesterone 200 mg three times daily.

Fertilization was performed using standard IVF/ICSI. Fertilization was successful in IVF when 1 or 2 pronuclei (PN) were observed in the oocyte's cytoplasm, in contrast to ICSI where 2 PN were indispensable in order to call fertilization successful. Fertilization rate was calculated by dividing the total number of fertilized eggs over the number of mature (metaphase II) oocytes.

Embryo transfer was carried out on Day 3 after oocyte aspiration.

A blood test to detect pregnancy was performed on day 15 after aspiration and was considered positive when ß-hCG > 5 UI/L. A second blood test was carried out 2 days later in the case of a positive test. A clinical pregnancy defined by "US visualization of one or more intra-uterine gestational sacs". (Zegers-Hochschild, 2017) was confirmed 3 weeks after the embryo transfer.

<u>**Timeline of treatment protocol**</u>



Primary outcome

The primary outcome in this study was the proportion of women who reached their optimal ovarian response defined as 5-15 matures oocytes.

Non-optimal response was observed in women with < 5 and >15 retrieved oocytes, or in women with cancelled oocyte pickup due to insufficient response. Were also included in this same category of non-optimal response women at risk of OHSS where either no oocyte pickup was performed or final maturation was completed but all embryos were frozen (freeze-all).

Secondary outcomes

Secondary endpoints included starting rFSH dose, dose adjustment rate, duration of stimulation, OHSS, clinical pregnancies and live birth rate per transfer. A clinical pregnancy is defined as: "a pregnancy diagnosed by ultrasound visualization of one or more gestational sacs, including ectopic pregnancy" (Zegers-Hochschild. 2017).

Statistical Analysis

The optimal response was arbitrarily set at 5-15 oocytes, in accordance with several previously published studies. Indeed, with less than 5 mature oocytes chances of obtaining good quality embryos are at stake, whereas when > 15 oocytes are retrieved the risk of OHSS increases (Ji et al.2016; Steward et al., 2014).

Having retrospectively analyzed study center Cliniques universitaires Saint-Luc's database, statistics showed that 56% of women are adequate responders (5-15 oocytes), therefore 44% of patients did not reach optimal response to controlled ovarian stimulation (38% < 5 oocytes and 6% > 15 oocytes).

In this study we aim to increase this percentage by 16%, leading to 72% of adequate responders which would be clinically significant to support the use of this algorithm in daily practice.

A sample size calculation showed that, in order to detect this increase between the groups with an 80% power, at significance level 0.05 using a chi-squared test, approximately 141 women reaching oocyte retrieval are required in each study group. In a conventional IVF/ICSI cycle, approximately 9% of women who start stimulation do not reach oocyte yield. Hence, to outweigh the cutback throughout the stimulation prosses, 154 women are required in each study group.

When analyzing results, a chi-squared test and a Fisher’s Exact test (for small numbers) were used in categorical data, and a Student t-test in continuous data.

Results

A total of 150 patients were included in the study so far for intermediate analysis of the risk-benefit balance and were randomized into study and control group: n=75 and n = 75, respectively. Couples were excluded from statistical analysis if they dropped out between recruitment and the start of stimulation. In the study group, 2 women were excluded for personal reasons versus 4 excluded patients in the control group (one spontaneous pregnancy and three for personal reasons) therefore the total number of women included in statistical analysis comprised of 73 women in the study group and 71 women in control group. Twenty-six women were randomized in study center in Beirut and 124 women at CUSL.

Patient characteristics were comparable between groups. As shown in Table 1, variables such as age, BMI, duration and type of infertility, smoking habits, day 3 FSH, AMH and AFC did not show significant differences. In both groups, the main cause of infertility was male factor (54/73, 74.0% in study group, 54/71, 76.1% in control group). Even though no statistical significance was shown, we did observe a higher amount of surgically extracted sperm in the study group (9/73, 12.3% vs 4/71, 5.6%; p = 0.24). Idiopathic causes came second in line with 11.0% in the study group and 12.7% in control group. When one unique cause was not attributable, and several factors came into account to being responsible for the infertility, couples were allocated to the mixed group which accounted for 7/73 in the study group and 4/71 in the control group. Finally, other infertility causes included mechanical factors and ovulatory dysfunction (3/73, 4.1% in study group vs 3/71, 4.2% in control group).

The proportion of women starting their first attempt of IVF/ICSI (50/73 in study group versus 62/71in control group), was significantly higher in control group (p = 0.008). In addition, a third or higher attempt was significantly lower in control group (p = 0.05).

Starting FSH doses were calculated according to the algorithm in the study group and using current practice (based on practitioner's experience in interpretation of medical records including age, basal FSH, AFC, AMH and results of previous treatments) in the control group. Stimulation results are presented in Table 2. Starting dose was to be maintained for the first 5 days in both groups, after which dose adaptations were allowed. Twenty-five women received < 150 IU per day as a starting dose in the group with algorithm, in contrast to 10 in controls; this difference was statistically significant p = 0.005. The proportion of women receiving a standard dose of 150 IU per day, was also significantly different in groups (5/73, 6.9% in study group versus 19/71, 26.8% in control group; p = 0.002). In contrast, no significant difference was observed in patients receiving > 150 < 300 UI/day (p = 0.23) and ≥ 300 IU/day (p = 0.1). (See Figure 2).

Dose adjustment (≥ 50 IU variation) after the fifth day of stimulation was observed in 21 patients in study group and 10 patients in control group.

A total of 17 patients (23.3%) had their dose increased in the study group, compared to 7 patients (9.9%) in the control group, and this difference was statistically significant (p = 0.04). Dose decreases did not reach statistical significance (p = 0.21). The duration of stimulation was comparable between the groups (10.5 +/- 2.9 days in study group; vs 10.0 +/- 3.3 days in control group; p = 0.37) as well as total dose of FSH administered (2013.7 +/- 903.7 in study group vs 2044.2 +/- 951.7; p = 0.84).

Oocyte aspiration was performed in 71 patients (97.3%) in study group and 70 patients (98.6%) in control group. One case of oocyte retrieval cancellation due to insufficient ovarian response was observed in study group. In each group one patient dropped out of the study during stimulation for personal reasons. In study and control group, at least one mature oocyte was reached in 97.2% and 94.3% of patients who went through with oocyte aspiration, respectively. A total of six women did not obtain any mature oocytes after aspiration: 2 women in study group and 4 women in control group. The mean number of mature oocytes was 6.4 +/- 4.3 in study group and 5.8 +/- 3.4 in control group; this difference was not significantly different (p = 0.38).

With regard to the primary outcome i.e. total number of mature oocytes, there was no significant difference. In the study and in the control group, less than 5 oocytes were retrieved in 26 and 25 patients, respectively (p = 0.96). The intended number of mature oocytes was achieved in 42 women (57.5%) in the study group and 40 women (56.3%) in the control group (p = 0.88). Figure 3 and 4.

In the study and the control group, a total of 5 women (6.8%) and 4 (5.6%) were at risk of OHSS with use of preventive measures such as use of a GnRH agonist (Decapeptyl®) to trigger ovulation, freeze-all or withdrawal from oocyte aspiration, respectively (Fishers exact p = 1). No cases of severe OHSS were observed in this trial.

Embryo transfer was performed in 66 women (90.4%) in study group, and 64 women (90.1%) in control group, with no statistical difference as to the number of embryos transferred.

Secondary outcomes are presented in Table 3 and were similar between groups. A clinical pregnancy was observed in 23/73 (31.5%) patients in study group and 29/71 (40.8%) in control group. Even though a higher proportion of live births per started stimulation cycle was observed in control group (18/71; 25.4% in control group vs 12/73, 16.4% in study group), no statistical difference was proven (p = 0.19). Live birth rate per transfer was 18.2% in study group and 28.1% in control group (p = 0.18).

Table 1. Patient characteristics (n=144) Parameters	Study group (n=73)	Control group (n=71)	χ^2	Ficher Exact
Age (mean +/- SD)	34.0 +/- 4.5	33.2 +/- 4.4	0.31	
BMI (kg/m2)	23.5 +/- 3.4	24.0 +/- 4.0	0.48	
Smokers (%)	12 (16.4)	16 (22.5)	0.36	
Duration of infertility (years)	3.2 +/- 2.8	3.0+/- 1.9	0.56	
Type of infertility (%)				
Primary	44 (60.3)	43(60.6)	0.97	
Secondary	29 (39.7)	28 (39.4)	0.97	
Cause of infertility (%)				
Male factors	54 (74.0)	54 (76.1)	0.77	
Ejaculated sperm	46 (61.6)	50 (70.4)	0.35	
TESE/PESA	9 (12.3)	4 (5.6)	0.16	0.24
Other (tubal, ovulation, uterine)	3 (4.0)	3 (4.2)	0.97	1
Mixed	8 (11.0)	5 (7.0)	0.41	0.56
Idiopathic	8 (11.0)	9 (12.7)	0.75	0.8
Number of previous IVF attempts (%)				
First attempt	50 (68.5)	62 (87.3)	0.006	0.008
Second attempt	14 (19.2)	7 (9.9)	0.1	0.2
Third attempt or >	9 (12.3)	2 (2.8)	0.03	0.05
Day 3 FSH, IU/L (mean +/- SD)	7.6 +/- 3.1	8.7 +/- 4.6	0.09	
AMH, ng/mL (mean +/- SD)	3.1 +/- 2.3	2.7 +/- 2.6	0.35	
Total AFC (2-10mm) (mean+/- SD)	8.6 +/- 4.3	7.4 +/- 4.5	0.10	
AFC 2-5 mm (mean +/- SD)	9.4 +/- 3.7	8.4 +/- 4.8	0.14	
AFC 6-10 mm (mean +/-SD)	7.8 +/- 4.7	6.5 +/- 4.1	0.06	

Figure 1. Flow chart of study population

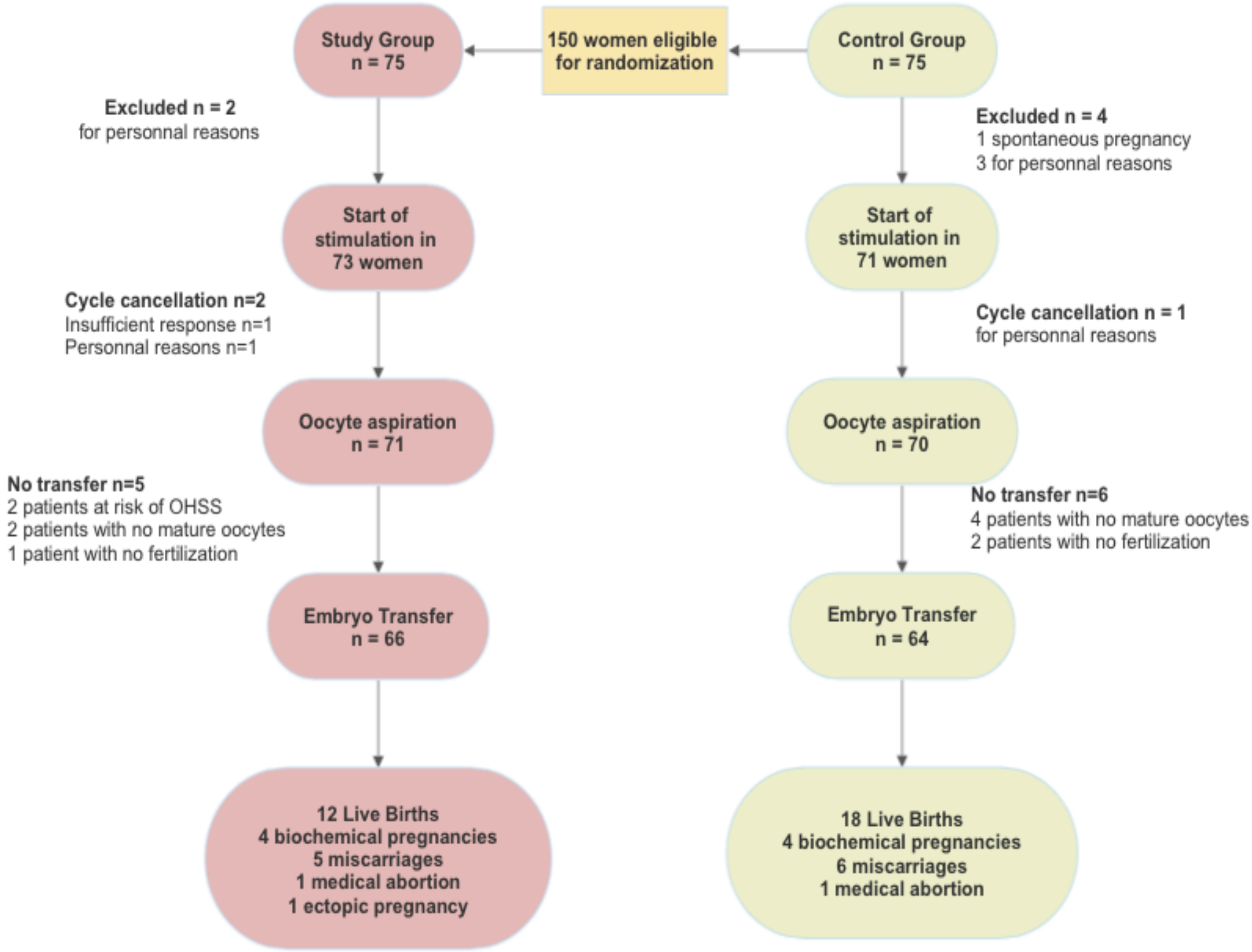


Table 2. Stimulation (n = 144) **Parameters**	Study group (n=73)	Control group (n=71)	χ^2	**Fisher Exact**
Starting rFSH dose (day 1-5)				
< 150 IU/day	25 (34.2)	10 (14.1)	0.005	
= 150 IU/day	5 (6.9)	19 (26.8)	0.001	0.002
>150 < 300 IU/day	35 (47.9)	27 (38.0)	0.23	
= 300 IU/day	4 (5.5)	15 (21.1)	0.006	0.007
> 300 IU/day	4 (5.5)	0	0.005	0.12
Dose adaptation (%)				
Increase (≥ 50IU)	17 (23.3)	7 (9.9)	0.03	0.04
Decrease (≥ 50IU)	4 (5.5)	3 (4.2)	0.72	1
Duration of stimulation, days (mean +/- SD)	10.5 +/- 2.9	10.0 +/- 3.3	0.37	
Total rFSH dose IU (mean +/- SD)	2013.7 +/- 903.7	2044.2 +/-951.7	0.84	
No Patients with oocyte aspiration (%)	71 (97.3)	70 (98.6)	0.58	1
No of aspirated oocytes (mean +/- SD)	8.1 +/-5.2	7.4 +/-4.1	0.38	
No Patients with mature oocytes (%)	69 (94.5)	66 (93.0)	0.70	0.74
No of mature oocytes (mean +/- SD)	6.4 +/- 4.3	5.8 +/- 3.4	0.37	
Mature oocytes (%)				
< 5	26 (35.6)	25 (33.3)	0.96	
5-15	42 (57.5)	40 (56.3)	0.88	
>15	2 (2.7)	1 (1.4)	0.58	1
Fertilization rate	0.74 +/-0.22	0.68 +/-0.23	0.2	
OHSS risk	5 (6.8)	4 (5.6)	0.76	1
OHSS				
Mild	3	2	0.67	1
Moderate	1	0	0.32	1
Severe	0	0		
IVF (%)	7/68 (10.3)	3/66 (4.5)	0.21	0.32
ICSI (%)	61/68 (89.7)	63/66 (95.5)	0.21	0.32
Embryo transfer (%)	66 (90.4)	64 (90.1)	0.96	1
1	32 (43.8)	38 (53.5)	0.25	
2	24 (32.9)	20 (28.2)	0.54	
>2	10 (13.7)	6 (8.5)	0.32	0.43

Figure 2. Starting rFSH dose (day 1-5)

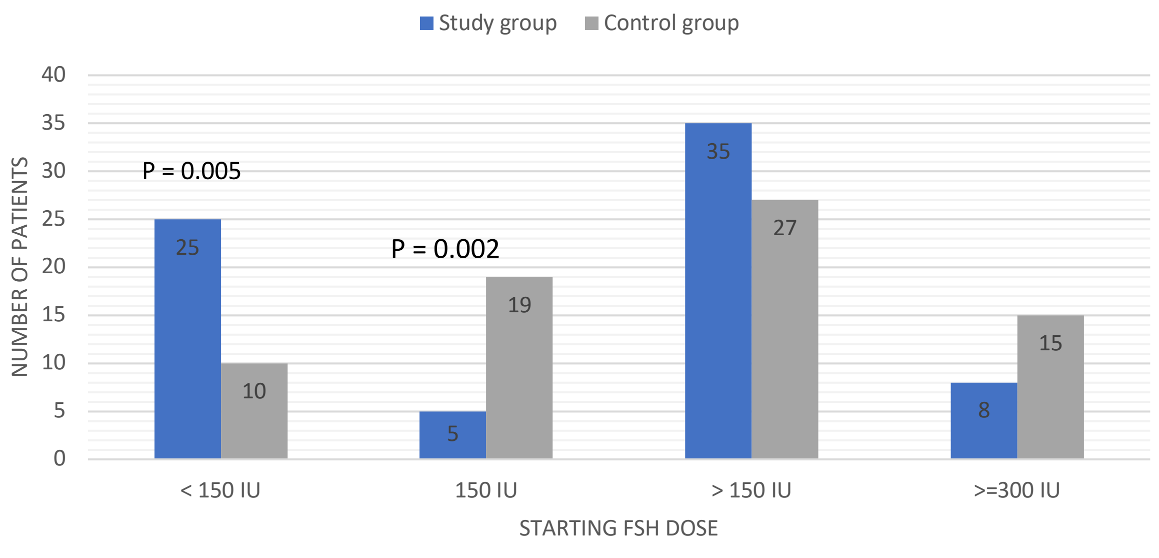
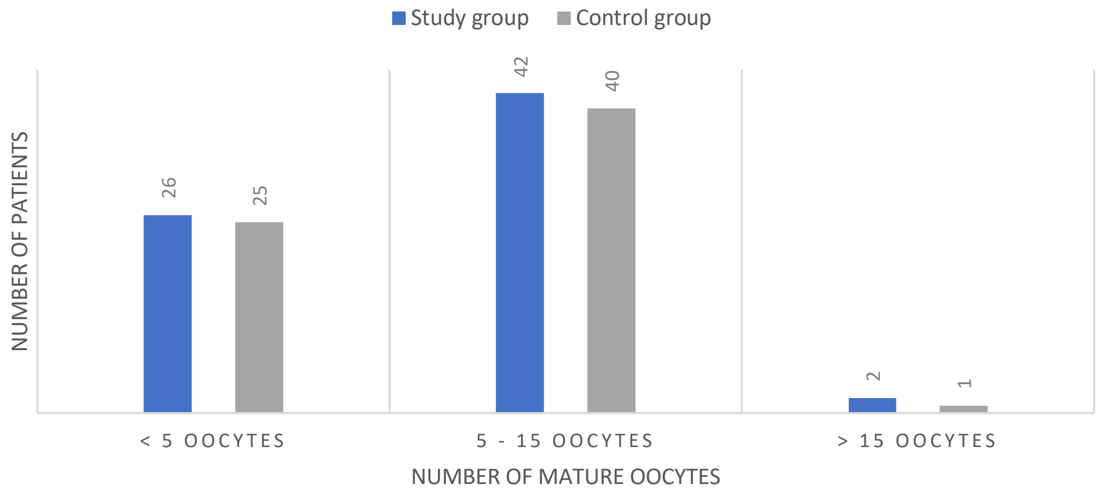


FIGURE 3. PRIMARY OUTCOME: NUMBER OF MATURE OOCYTES



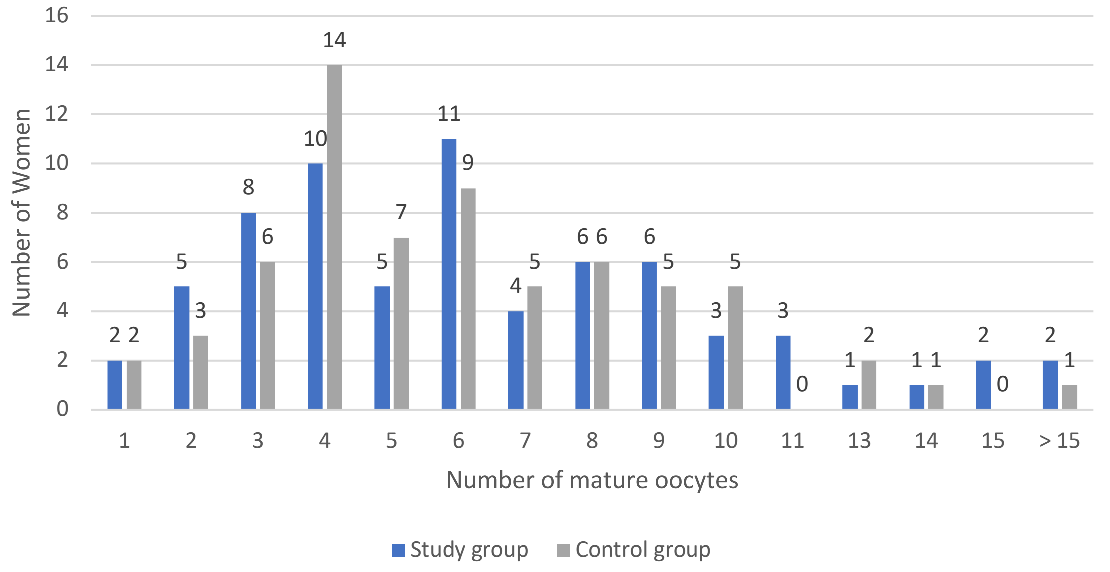


Figure 4. Primary outcome: number of mature oocytes

Table 3. Secondary outcomes (n=144)

Parameters	Study group (n=73)	Control group (n=71)	χ^2	**Fisher Exact**
Biochemical pregnancy (%)	4 (5.5)	4 (5.6)	0.97	1
Ectopic pregnancy (%)	1 (1.4)	0 (0.0)	0.32	1
Miscarriage (%)	4 (5.5)	5 (7.0)	0.70	0.74
Medical abortion (%)	1 (1.4)	1 (1.4)	0.98	1
Live birth rate per started cycle (%)	12 (16.4)	18 (25.4)	0.19	
Live birth rate per transfer (%)	12 (18.2)	18 (28.1)	0.18	

Figure 5. Study group: number of women with optimal response compared to low or excessive response

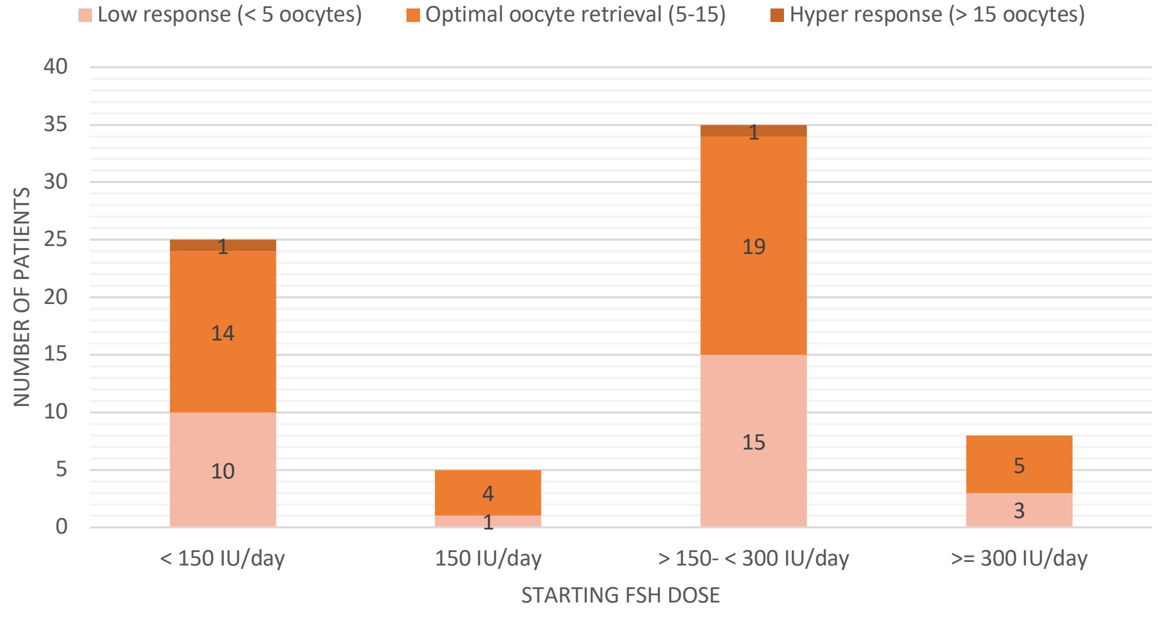
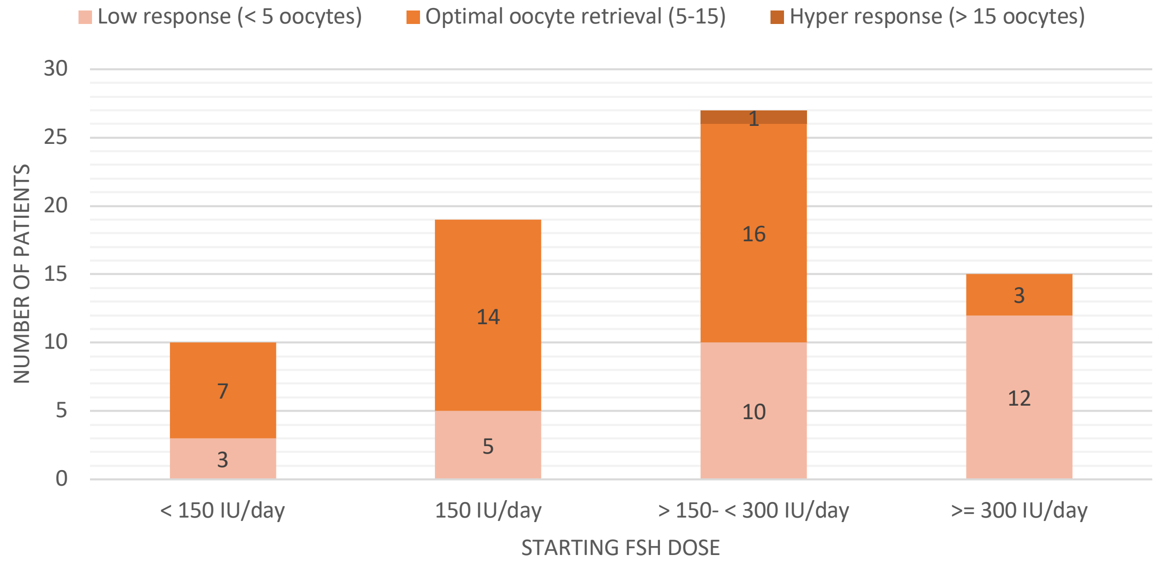


Figure 6. Control group: number of women with optimal response compared to low or excessive response



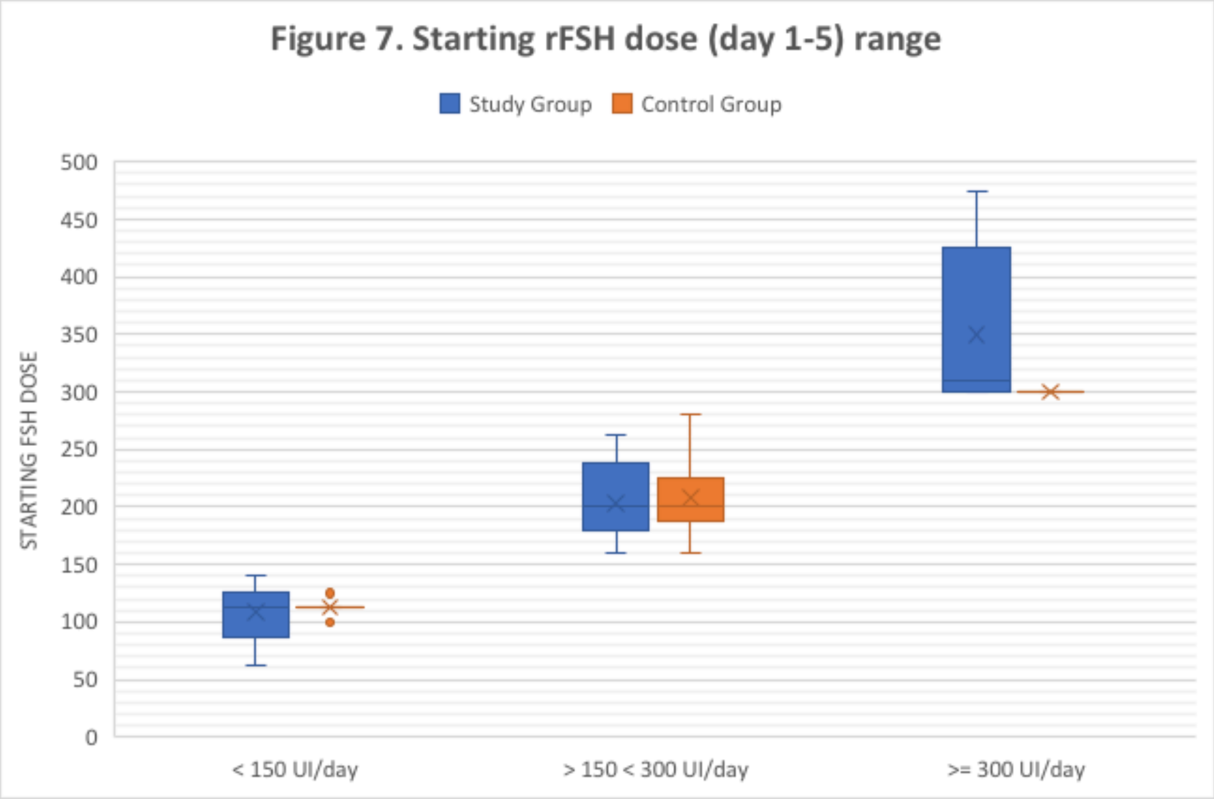


Figure 7. Starting rFSH dose (day 1-5) range

Table 4. Study group primary + secondary outcomes analyzed in four starting FSH categories (number of patients and %)

Study group	*< 150 IU/day*	*150 IU/day*	*> 150 - < 300 IU/day*	*>= 300 IU/day*
Optimal response (5-15 oocytes)	14/25 (56%)	4/5 (80%)	19/35 (54%)	5/8 (63%)
Dose increase	10/25 (40%)	3/5 (60%)	4/35 (11%)	0/8 (0%)
Dose decrease	0/ 25 (0%)	0/5 (0%)	4/35 (11%)	0/8 (0%)
Average daily dose IU (mean +/- SD)	108.5 +/- 22.4	150 +/- 0	202 +/- 30.8	350 +/- 67.6
Starting FSH dose range IU (lowest-highest)	62.5-140	0	160-262.5	300-475
Duration of stimulation in days (mean+/- SD)	11.2 +/- 2.0	13.6 +/- 4.8	9.6 +/- 2.2	10.1 +/- 1.3
Live births per started cycle	4/25 (16%)	0/5 (0%)	6/35 (17%)	2/8 (25%)

Table 5. Control group primary + secondary outcomes analyzed in four starting FSH categories (number of patients and %)

Control group	*< 150 IU/day*	*150 IU/day*	*> 150 - < 300 IU/day*	*>= 300 IU/day*
Optimal response (5-15 oocytes)	7/10 (70%)	14/19 (74%)	16/27 (59%)	3/15 (20%)
Dose increase	2/10 (20%)	2/19 (11%)	3/27 (11%)	0/15 (0%)
Dose decrease	0/10 (0%)	0/19 (0%)	3/27 (11%)	0/15 (0%)
Average daily dose IU (mean +/- SD)	112.5 +/- 5.3	150 +/- 0	208 +/- 27.8	300 +/- 0
Starting FSH dose range IU (lowest-highest)	100-125	0	160-280	0
Duration of stimulation in days (mean+/- SD)	12.0 +/- 6.5	9.6 +/- 1.7	9.5 +/- 2.1	10.2 +/- 2.9
Live births per started cycle	2/10 (20%)	4/19 (21%)	7/27 (26%)	5/15 (33%)

Discussion

In this prospective randomized study, a patient-individualized dosing algorithm was tested in order to asses it's clinical applicability and utility. It assigned each patient a personal starting rFSH dose, based on AFC (subpopulation of 2-5mm sized follicles), AMH and BMI.

The main hypothesis made was that the use of the algorithm would help decrease the proportion of insufficient and excessive responders (<5 and > 15 oocytes), decreasing the risk of hyperstimulation and opting for an increase of live births per egg retrieval which is the most important endpoint to patients.

Patients who underwent individualized dose did not achieve a higher proportion of mature oocytes than in the standard dosing regimen. In the study group 57.5% of patients obtained optimal oocyte retrieval set at 5 – 15; and 56.3% in the control group. These results were comparable with annual statistics reported at Cliniques universitaires Saint-Luc where approximately 56% of women retrieve between 5 and 15 mature oocytes. In present day practice, a physician tends to automatically personalize treatment through a profound anamnesis, physical examination and additional medical tests, which may explain that the utility of this algorithm is limited in the hands of an experimented specialist. On the other hand, it may be useful when initiating clinical practice and learning how to juggle with the various information.

Clearly, significantly more patients had a dose adjustment on day 6 in study group. Altogether 23.3% of the patients in study group had an increase of >= 50 IU on day 6, versus an 9.9% increase in control group (p = 0.04).

The algorithm appeared to have a disadvantage in predicting the starting dose of FSH in women with expected higher response to ovarian stimulation. As shown in tables 4-5, amongst the dose group < 150 IU/day, we observed in study group a much wider range in the starting FSH dose (from 62.5 IU/day up to 140 IU/day in study group versus 100 to 125 IU/day in control group); see box plot (Figure 7). In fact, when individualizing treatment, doses as low as 62.5 IU/day were assigned to patients, in contrast to control group where minimal starting dose was 100 IU/day. This may explain the significantly higher proportion of women who needed a dose increase in these two dose categories (<150 IU/day and =150 IU/day): 43% (13/30) increase in study group vs 14% (4/29) in control group (p = 0.01). Data per categories of starting FSH dose are presented in tables 4 and 5.

The correction factor used in the algorithm on basis of ovarian reserve markers (AMH and AFC 2-5mm) strongly impacts the starting dose calculated in women with high ovarian reserve. Hence, the lower dose of FSH administered in the population of patients with a high ovarian reserve increases insufficient ovarian response to stimulation and thereby the need to increase the FSH dose at day 6.

Interestingly, this increased need to adapt the dose on day 6 in study group in low dose groups (<150 IU/day and =150 IU/day) did not seem to have -in this intermediate study analysis- an impact on the final follicle recruitment and growth as no significant difference neither in the number of patients with the targeted number of oocytes is observed (18/30 in study group versus 21/29 in controls; $p = 0.3$), nor in the total stimulation days was observed. Nevertheless, in order to analyze if the dose increase was actually necessary and if it was proportional to the need between groups, a day 6 follicle analysis will be undertaken in a further investigation. This follicle analysis will allow to explore under what criteria dose increase was undertaken, if dose should have been increased more often in controls, thus if a potential bias as to dose increase exists between groups.

Our findings are consistent with previous published research. In studies with a minimum starting dose of 100IU/day, the percentage of women who responded poorly after stimulation and who’s cycle got cancelled were lower than in other studies where initial dose was < 100 IU/day (Popovic-Todorovic et al. 2003; Allegra et al. 2017). Indeed, as elaborated in CONSORT trial, doses as low as 37.5 IU/day resulted in a 100% cancellation rate and doses at 75 IU/day in a 25% cancellation rate (Oliviennes et al.2009). In the same direction, in our study, women with such low starting dose needed a dose increase at day 6 in order to boost follicle growth.

This might suggest that a set minimal starting dose of rFSH (e.g 100 IU/day) could be useful to lower the need to increase the rFSH dose on day six of the stimulation and hence achieve a faster follicle recruitment and growth. It is interesting to notice that almost all patients receiving <100 IU/day have an AMH that is > 2.5 ng/mL. With such a high AMH, the correction factor in the algorithm reduces dose by half which might underestimate the required starting FSH dose. Even though patients with a high AMH have a higher ovarian reserve and therefore an increased potential of recruitable follicles, a threshold value of FSH might still be necessary in order to recruit them. A slight modification in algorithm could be beneficial in this regard.

Another recently published RCT, using dosing algorithm based exclusively on AMH showed that amongst patients with an expected high response (AMH > 24 pmol/L), the reduction of starting rFSH dose to 100 IU/day as compared to a standard 150 IU/day dose significantly increased the proportion of poor responders (38% in study group vs 6% in control group, p = 0.029). (Petersen et al. 2019).

Similarly, the OPTIMIST study showed that in expected high responders based exclusively on AFC (AFC > 15), lowering the dose to 100 IU/day (vs a standard 150 IU/day) increased significantly patients with insufficient follicle growth and the need to increase rFSH doses throughout the study. (Oudshoorn et al. 2017).

On the other hand, in our study in >=300 IU/day category we observed significantly fewer poor responders in the study group. Sixty-three percent (5/8) of patients in study group reached optimal oocyte yield versus only 20% (3/15) in control group (p = 0.04); but this was not correlated with live births (25% vs 33% of live births, respectively). Considering the limited sample size, statistical power is poor, and results should be interpreted with caution for the time being. Additionally, statistical significance was observed as regards to daily dose of rFSH administered between groups: mean of 350 IU/day +/- 67.6 in study group versus 300 IU/day +/- 0 in control group (p = 0.01).

Hence, our algorithm was able to predict a category of patients who needed a higher starting dose of rFSH administration; reaching an overall better oocyte retrieval (compared to the same category in the control group) and an overall better live birth rate (compared to the lower starting dose categories in the study group). A larger patient population is needed to confirm or reject this hypothesis.

Similarly, in the second part of the OPTIMIST study, in predicted poor responders (AFC<11) by increasing doses up to 450 IU/day as compared to 150 IU/day, a higher oocyte yield, embryo transfer and a lower cancellation rate were observed. Conversely, the live birth rate was altogether not significantly increased (Van Tilborg et al.2017).

This study's substantial strength is its broad eligibility criteria and its generalizability to a wide population of patients. (e.g. poor responders, rank of attempt as there was no limit as to number of previous attempts)

The choice to not limit the trial to patients beginning their first IVF/ICSI cycle is worth mentioning. In fact, in all of the previously mentioned IVF dosing algorithm trials, entering a first IVF/ICSI cycle was a criterion for eligibility. In our study, only 68.5% and 87.3% of patients in study and control group started their first IVF/ICSI attempt, respectively. However, the difference between groups was statistically significant (p = 0.008, Fishers exact test) which could also induce a selection bias (either were higher rank attempts the sign of a poor prognosis or in the case of a previous successful attempt a better prognosis).

These findings lead us to thinking that an algorithmically calculated starting FSH dose might be most beneficial when no previous knowledge as to ovarian response is established. However, when ovarian response to stimulation has been identified by means of a first or second previous attempt, the clinician's personal experience could be better at predicting the starting FSH dose.

To the best of our knowledge, this is the third trial which used a GnRH antagonist to individualize gonadotropin dose. Recent studies suggest that there is a significantly higher risk of severe and moderate OHSS in GnRH agonist as compared to a GnRH antagonist treatment regimen (Toftager et al. 2016) and a benefit as to cumulative live birth rate with a minimum of a two-year follow-up with the antagonist protocol (Toftager et al. 2017). A meta-analysis published in 2014 including 23 RCTs, showed that OHSS incidence was significantly lower in an antagonist protocol as compared to an agonist one. However, even though it was shown that total oocyte yield was significantly diminished in the antagonist protocol, LBR was not different between protocols (Jin-song X et al, 2014). ESTHER trial was the first dose individualization study to use a GnRH antagonist, pointing to fewer patients requiring OHSS preventives measures in ART ($p = 0.01$) (Nyboe Andersen et al. 2017). In our study cases of OHSS and OHSS preventive measures were scarce and statistics did not point to any differences between study groups. There is no doubt that further studies are necessary to compare these different regimens and their potential implication in an individualized dosing treatment protocol.

In conclusion, the main question still remains to whether there is a benefit in continuing research of individualisation techniques and if physicians should finally depend on these dosing algorithms in day to day practice.

The main findings in this trial are coherent with other recent published studies. To this day, even though individualizing FSH dose with the new algorithm demonstrates an acceptable oocyte retrieval, it does not prove superiority as compared to a standard practice in hands of specialists in the field.

To this day, less than half of the number needed to treat has been included in the trial; which is currently a major limitation worth mentioning. It is indisputable that other questions will arise once the required total study population will be analysed.

References

Allegra A, Marino A, Volpes A, Coffaro F, Scaglione P, Gullo S et al. A randomized controlled trial investigating the use of a predictive nomogram for the selection of the FSH starting dose in IVF/ICSI cycles. Reprod Biomed Online. 2017 Apr;34(4):429-438. Available from : doi: 10.1016/j.rbmo.2017.01.012

“ART Fact sheet, 2014” European Society of Human Reproduction and Embryology

Berkkanoglu M, Ozgur K. What is the optimum maximal gonadotropin dosage used in microdose flare-up cycles in poor responders? Fertil Steril 2010; 94:662665.

Boots, C., & Stephenson, M. (2011). Does Obesity Increase the Risk of Miscarriage in Spontaneous Conception: A Systematic Review. Seminars in Reproductive Medicine, 29(06), 507–513. Available from: doi:10.1055/s-0031-1293204

Broer SL, Dólleman M, van Disseldorp J, Broeze KA, Opmeer BC, Bossuyt PM et al. Prediction of an excessive response in in vitro fertilization from patient characteristics and ovarian reserve tests and comparison in subgroups: an individual patient data meta-analysis. Fertility & Sterility 2013 Aug;100(2):420-9.e7. Available from : doi: 10.1016/j.fertnstert

Bungum L, Tagevi J, Jokubkiene L, Bungum M, Giwercman A, Macklon N et al. The impact of the Biological Variability or Assay Performance on AMH Meausurements: A Prospective cohort Study with AMH tested on three analytical assay-platforms. Frontiers in Endocrinology 2018. Available from: doi: 10.3389/fendo.2018.00603

Cai QF, Wan F, Huang R, Zhang HW. Factors predicting the cumulative outcome of IVF/ICSI treatment: a multivariable analysis of 2450 patients. Hum Reprod. 2011 Sep;26(9):2532-40. Available from: doi: 10.1093/humrep/der228

Christensen MW, Ingerslev HJ, Degn B, Kesmodel US. Effect of Female Body Mass Index on Oocyte Quantity in Fertility Treatments (IVF): Treatment Cycle Number Is a Possible Effect

Modifier. A Register-Based Cohort Study. 2016. Available from: doi: 10.1371/journal.pone.0163393

Clark AM, Thornley B, Tomlinson L, Galletley C, Norman RJ. Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. Human Reproduction. 1998 Jun;13(6):1502-5. Available from: doi: 10.1093/humrep/13.6.1502

Drakopoulos P, Blockeel C, Stoop D, Camus M, de Vos M, Tournaye H, et al. Conventional ovarian stimulation and single embryo transfer for IVF/ICSI. How many oocytes do we need to maximize cumulative live birth rates after utilization of all fresh and frozen embryos? Hum Reprod. 2016 Feb;31(2):370-6. Available from : doi : 10.1093/humrep/dev316

Ferraretti AP, La Marca A, Fauser BCJM, Tarlatzis B, Nargund G Gianaroli L et al.
ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: The Bologna criteria. Human Reproduction 2011, 26:1616-1624.

Gomez R, Schorsch M, Hahn T, Henke A, Hoffmann I, Seufert R et al. The influence of AMH on IVF success. Arch Gynecol Obstet. 2016 Mar;293(3):667-73. Available from : doi: 10.1007/s00404-015-3901-0

Hamdine O, Eijkemans MJ, Lentjes EW, Torrance HL, Macklon NS, Fauser BC, et al. Ovarian response prediction in GnRH antagonist treatment for IVF using anti-Müllerian hormone. Human Reproduction. 2015 Jan;30(1):170-8. Available from: doi: 10.1093/humrep/deu266

Howles CM, Saunders H, Alam V, Engrand P. Predictive factors and a corresponding treatment algorithm for controlled ovarian stimulation in patients treated with recombinant human follicle stimulating hormone (follitropin alfa) during assisted reproduction technology (ART) procedures. An analysis of 1378 patients. Curr Med Res Opin. 2006 May;22(5):907-18. https://www.ncbi.nlm.nih.gov/pubmed/16709312 Available from: doi: 10.1185/030079906X104678

Humaidan P, Alviggi C, Fisher R, Esteves SC. The Novel POSEIDON stratification of low prognosis patients in Assisted Reproductive Technology and its proposed marker of successful outcome. F1000Research 2016;5:2911.

Ji J, Liu Y, Tong XH, Luo L, Ma J, Chen Z. The optimum number of oocytes in IVF treatment: an analysis of 2455 cycles in China. Human Reproduction. 2013 Oct;28(10):2728-34. https://www.ncbi.nlm.nih.gov/pubmed/23887075 Available from: doi: 10.1093/humrep/det303

Xiao J, Su C, Zeng X. Comparisons of GnRH Antagonist versus Agonist Protocol in supposed normal ovarian responders undergoing IVF: a systematic review and meta-analysis. PLoS One. 2014; 9(9): e106854. Available from: doi: 10.1371/journal.pone.0106854

Kumar P., Farouk Sait S., Sharma A., Kumar M. Ovarian hyperstimulation syndrome. J Hum Reprod Sci. 2011 May-Aug; 4(2): 70–75. Available from: doi: 10.4103/0974-1208.86080

La Marca A, Sunkara SK. Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice. Human Reproduction Update, Volume 20, Issue 1, 1 January 2014, Pages 124–140. Available from: doi: 10.1093/humupd/dmt037

Magnusson A, Nilsson L, Oleröd G, Thurin-Kjellberg A, Bergh C. The addition of anti-Müllerian hormone in an algorithm for individualized hormone dosage did not improve the prediction of ovarian response-a randomized, controlled trial. Hum Reprod. 2017 Apr 1;32(4):811-819. Available from : doi: 10.1093/humrep/dex012

Nelson SM, Yates RW, Fleming R. Serum anti-Müllerian hormone and FSH: prediction of live birth and extremes of response in stimulated cycles: implications for individualization of therapy. Hum Reprod. 2007 Sep;22(9):2414-21. Available from : doi: 10.1093/humrep/dem204

Nelson S, Larsson P, Mannaerts B, Nyboe Andersen A, Fauser B. Anti-Müllerian hormone variability and its implications for the number of oocytes retrieved following individualized dosing with follitropin delta. Clinical Endocrinology. 2019;90:719–726

NyboeAndersen A, Nelson SM, Fauser BC, Velasco JA, Klein BM, Arce JC. Individualized versus conventional ovarian stimulation for in vitro fertilization: a multicenter, randomized, controlled, assessor-blinded, phase 3 noninferiority trial. Fertility and Sterility. Volume 107, Issue 2, February 2017, Pages 387-396.e4. Available from : doi : 10.1016/j.fertnstert.2016.10.033

Olivennes F, Howles CM, Borini A, Germond M, Trew G, Wikland M et al. Individualizing FSH dose for assisted reproduction using a novel algorithm: the CONSORT study. Reproduction Biomed Online. 2009 Feb;18(2):195-204. Available from : doi : 10.1016/s1472-6483(10)60256-8

Oudshoorn SC, Van Tilborg TC, Eijkemans MJ, Oosterhuis GJ, Friederich J, Van Hooff MH et al. Individualized versus standard FSH dosing in women starting IVF/ICSI: an RCT. Part 2: The predicted hyper responder. Human Reproduction, Volume 32, Issue 12, 1 December 2017, Pages 2506–2514. Available from: doi: 10.1093/humrep/dex319

Popovic-Todorovic B, Loft A, Bredkjaeer HE, Bangsbøll S, Nielsen IK, Andersen AN. A prospective randomized clinical trial comparing an individual dose of recombinant FSH based on predictive factors versus a 'standard' dose of 150 IU/day in 'standard' patients undergoing IVF/ICSI treatment. Human Reproduction. 2003 Nov;18(11):2275-82.

Rich-Edwards, J. W., Spiegelman, D., Garland, M., Hertzmark, E., Hunter, D. J., et al.
(2002). Physical Activity, Body Mass Index, and Ovulatory Disorder Infertility.
Epidemiology, 13(2), 184–190. Available from: doi:10.1097/00001648-200203000-00013

Rittenberg V, Seshadri S, Sunkara SK, Sobaleva S, Oteng-Ntim E, El-Toukhy T. Effect of body mass index on IVF treatment outcome: an updated systematic review and meta-analysis. Reprod Biomed Online. 2011 Oct;23(4):421-39. Available from: doi: 10.1016/j.rbmo.2011.06.018

Sneed ML, Uhler ML, Grotjan HE, Rapisarda JJ, Lederer KJ, Beltsos AN. Body mass index: impact on IVF success appears age-related. Human Reproduction. 2008. Aug;23(8):1835-9. Available from : doi: 10.1093/humrep/den188

Steward RG, Lan L, Shah AA, Yeh JJ, Price TM, Goldfarb JM et al. Oocyte number as a predictor for ovarian hyperstimulation syndrome and live birth: an analysis of 256,381 in vitro fertilization cycles. Fertil Steril. 2014 Apr;101(4):967-73. Available from: doi: 10.1016/j.fertnstert.2013.12.026

Tan R, Pu D, Liu L, Liu J, Wu J. Comparisons of inhibin B versus antimüllerian hormone in poor ovarian responders undergoing in vitro fertilization. Fertility and Sterility. Volume 96, Issue 4, October 2011, Pages 905-911.e2. Available from: doi: 10.1016/j.fertnstert.2011.07.1102

Van Tilborg TC, Torrance HL, Oudshoorn SC, Eijkemans MJ, Koks CA, Verhoeve HR et al. Individualized versus standard FSH dosing in women starting IVF/ICSI: an RCT. Part 1: The predicted poor responder. Human Reproduction, Volume 32, Issue 12, 1 December 2017, Pages 2496–2505. Available from: doi: 10.1093/humrep/dex318

Wittemer C, Ohl J, Bailly M, Bettahar-Lebugle K, Nisand I. Does body mass index of infertile women have an impact on IVF procedure and outcome? J Assist Reprod Genet. 2000 Nov;17(10):547-52. Available from: doi: 10.1023/a:1026477628723

Wiweko B, Prawesti DM, Hestiantoro A, Sumapraja K, Natadisastra M, Baziad A. Chronological age vs biological age: an age-related normogram for antral follicle count, FSH and anti-Mullerian hormone. J Assist Reprod Genet. 2013 Dec;30(12):1563-7. Available from : doi: 10.1007/s10815-013-0083-1

UNIVERSITÉ CATHOLIQUE DE LOUVAIN
Faculté de médecine et médecine dentaire
Avenue Mounier, 50 bte B1.50.04, 1200 Woluwe-Saint-Lambert, Belgique | **www.uclouvain.be/mede**