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Impact of oocyte maturation triggers in high-responders: a report on 1239 consecutive ART treatment cycles

Maria da Silva Gonçalves

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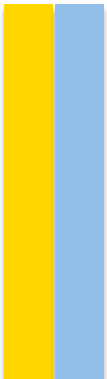

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Mestrado Integrado em Medicina
Instituto de Ciências Biomédicas Abel Salazar
Universidade do Porto
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Scientific Integrity Declaration

All Authors participated in the present study and have seen and approved the final version of this manuscript. There was no fabrication, falsification, plagiarism, repetitive publications, obfuscation, or human or animal experimentation performed to elaborate this work.

All Authors disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence their work, such as manufacturers of pharmaceuticals, laboratory supplies, and/or medical devices. It also includes employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding, including any financial arrangement with a company whose product is prominent in the submitted manuscript or with a company making a competing product, and any commercial affiliations. The authors have no connection to any companies or products mentioned in this manuscript.

Porto, June 2nd 2024

Maria da Silva Gonçalves

Mário Manuel da Silva Leite Sousa

To my mother, my father, my wonderful siblings, and my lovely friends, who have carried me through this long journey that is, trully, just beginning.

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Work Recognition

In poster format, selected parts of the present work were presented at the 9° Congresso Português de Medicina da Reprodução and were chosen to be orally presented at the conference.

This work also contributed to a poster presentation at the 17th Encontro de Investigação Jovem da U.Porto (IJUP). Respective supportive documents are presented as Annexes.

Resumo

Objetivo: Analisar, numa população de altas-respondedoras, os efeitos da indução da maturação ovocitária com gonadotrofina coriónica humana (hCG) ou um agonista da hormona libertadora de gonadotrofinas (aGnRH), com hCG na fase lútea, nas taxas de síndrome de hiperestimulação ovárica (SHO) e nos resultados embriológicos, clínicos e neonatais.

Desenho: Estudo coorte retrospectivo observacional.

Contexto: Centro privado de fertilidade.

Paciente(s): 652 pacientes altas-respondedoras e resultados clínicos.

Exposição: Indutor da maturação ovocitária.

Principais Resultado(s) Avaliados: Taxas de SHO, gravidez clínica, gravidez evolutiva, parto de nado-vivo, recém-nascidos, e resultados clínicos cumulativos.

Resultado(s): 652 pacientes altas-respondedoras foram submetidas a 705 ciclos de transferência de embriões a fresco e 534 ciclos de transferência de embriões criopreservados. Dos ciclos a fresco, 232 usaram hCG e 473 um aGnRH como indutor da maturação ovocitária. Não foram encontradas diferenças significativas entre os grupos (hCG *vs.* aGnRH) em relação às taxas de SHO (3.9% *vs.* 3.4%) ou de hospitalização por SHO (1.3% *vs.* 0.6%). Não ocorreu SHO grave sob *freeze-all*. Em relação aos resultados embriológicos, o grupo aGnRH evidenciou um número significativamente superior de complexos *cumulus*-ovócitos obtidos, maior taxa de formação de blastocistos, e um número significativamente menor de embriões transferidos. Não foram observadas diferenças significativas nas taxas de fertilização, clivagem de embriões, embriões de elevada qualidade ou transferência de embriões por dia. Considerando os resultados clínicos, o grupo aGnRH apresentou taxas significativamente superiores de gravidez clínica (51.9% *vs.* 60.9%, p=.042) e implantação, e uma taxa significativamente inferior de gestações gemelares. Não houve diferenças significativas entre os grupos em relação às taxas de gravidez ectópica, abortamento, gravidez evolutiva (43.3% *vs.* 48.9%), parto de nado-vivo (42.8% *vs.* 48.9%) e recém-nascidos (53.8% *vs.* 53.5%). A taxa cumulativa de gravidez clínica foi significativamente maior no grupo aGnRH (69.4% *vs.* 82.5%, p<.001), mas não foram observadas diferenças significativas entre os grupos em relação às taxas cumulativas de gravidez evolutiva (58.3% *vs.* 64.7%), parto de nado-vivo (57.8% *vs.* 64.3%) ou recém-nascidos (70.7% *vs.* 70.2%). Após ajuste, não foram encontradas diferenças significativas.

Conclusão(ões): Em pacientes altas-respondedoras, embora não tenha abolido a SHO, o uso de um aGnRH foi associado a taxas superiores de formação de blastocistos, implantação, gravidez clínica e gravidez clínica cumulativa. Contudo, após regressão logística multivariada, não existiram diferenças significativas. Para abolir a SHO, sugere-se a utilização de um único critério consensual para selecionar o indutor da maturação ovocitária e que o *freeze-all* deva ser aplicado a todos os casos suspeitos de SHO.

Palavras-chave: altas-respondedoras, procriação medicamente assistida, indutor da maturação ovocitária, síndrome de hiperestimulação ovárica, resultados clínicos

Abstract

Objective: To study, in a high-responder population, the effects of triggering oocyte maturation with human choriogonadotropin (hCG) or a gonadotropin-releasing hormone agonist (GnRH-agonist), with luteal hCG, on the rates of ovarian hyperstimulation syndrome (OHSS), and in embryological, clinical and newborn outcomes.

Design: Retrospective observational cohort study.

Setting: Private infertility center.

Patient(s): 652 high-responder patients and their clinical outcomes.

Exposure: Oocyte maturation trigger.

Main Outcome Measure(s): OHSS, clinical pregnancy, ongoing pregnancy, livebirth delivery, and newborn rates, with respective cumulative clinical outcomes.

Result(s): 652 high-responder patients underwent 705 fresh embryo transfer cycles and 534 frozen embryo transfer cycles. Of the fresh embryo transfer cycles, 232 used hCG and 473 a GnRH-agonist as a trigger. No significant differences between groups (hCG *vs.* GnRH-agonist) were found concerning OHSS (3.9% *vs.* 3.4%) or OHSS hospitalization (1.3% *vs.* 0.6%) rates. No severe OHSS occurred under freeze-all. Regarding embryologic outcomes, the GnRH-agonist group evidenced a significantly higher mean number of retrieved *cumulus*-oocyte complexes and blastocyst formation rate, and a significantly lower number of transferred embryos. No significant differences were observed in the fertilization, embryo-cleavage, high-quality embryos, or embryo transfer day rates. Considering clinical outcomes, the GnRH-agonist group presented significantly higher rates of clinical pregnancy (51.9% *vs.* 60.9%, p=.042) and implantation, and a significantly lower rate of twin pregnancies. There were no significant differences between groups concerning the ectopic pregnancy, abortion, ongoing pregnancy (43.3% *vs.* 48.9%), livebirth delivery (42.8% *vs.* 48.9%), and newborn (53.8% *vs.* 53.5%) rates. The cumulative clinical pregnancy rate was significantly higher in the GnRH-agonist group (69.4% *vs.* 82.5%, p<.001), but no significant differences between groups were observed regarding the cumulative rates of ongoing pregnancy (58.3% *vs.* 64.7%), livebirth delivery (57.8% *vs.* 64.3%) or newborn (70.7% *vs.* 70.2%). After adjusting for age, AMH, and follicles, no significant differences were found between groups.

Conclusion(s): Although not abolishing OHSS, the use of a GnRH-agonist as a trigger in high-responders was associated with higher blastocyst formation, implantation, clinical pregnancy, and cumulative clinical pregnancy rates. However, multivariable logistic regression analysis revealed no significant differences. Additionally, to abolish OHSS, data suggests the need for a sole consensus criterion to select the oocyte maturation trigger, and that freeze-all should be applied to all suspected OHSS cases.

Keywords: high responders, assisted reproduction technologies, oocyte maturation trigger, ovarian hyperstimulation syndrome, clinical outcomes

Abbreviation List

AMH - anti-Müllerian hormone
ART - assisted reproduction technologies
bFSH - basal follicle-stimulating hormone
βhCG - beta human chorionic gonadotropin
bLH - basal luteinizing hormone
BMI - body mass index
BP - biochemical pregnancy
CNPMA - Conselho Nacional de Procriação Medicamente Assistida
COC - cumulus-oocyte complexes
COS - controlled ovarian stimulation
CP - clinical pregnancy
DS - diluent solution
E2 - estradiol
ETC - embryo transfer cycle
FET - frozen-thawed embryo transfer
FSH - follicle-stimulating hormone
GnRH - gonadotropin-releasing hormone
GnRHa - gonadotropin-releasing hormone agonist
hCG - human chorionic gonadotropin
ICSI - intracytoplasmic sperm injection
IVF - in-vitro fertilization
LBD - live birth delivery
LH - luteinizing hormone
NB - newborn
OHSS - ovarian hyperstimulation syndrome
OP - ongoing pregnancy
P4 - progesterone
PCOS - polycystic ovary syndrome
PGT - preimplantation genetic testing
rFSH - recombinant follicle-stimulating hormone
rhCG - recombinant human chorionic gonadotropin
RT - room temperature
SPM - sperm preparation medium
TESE - testicular sperm extraction
TESA - testicular sperm aspiration
TS - thawing solution
WHO - World Health Organization
WS - washing solution

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Impact of oocyte maturation triggers in high-responders: a report on 1239 consecutive ART treatment cycles

Running Title

Trigger's impact in high-responders

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Conflict of interest statement for all authors

The authors declare that they have no competing interests. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could constitute as a potential conflict of interest. The study's sponsors were not involved in the study design, the collection, analysis, and interpretation of data, the writing of the report, or in the decision to submit the article for publication. The corresponding author had full access to all the data in the study and had final responsibility to submit for publication.

Attestation statements

Data regarding any of the subjects in the study have not been previously published unless specified.

M.G. has nothing to disclose. M.C. has nothing to disclose. J.T.S. has nothing to disclose. J.S. has nothing to disclose. P.V. has nothing to disclose. C.O. has nothing to disclose. M.F.C. has nothing to disclose. A.B. has nothing to disclose. M.S. has nothing to disclose

Data sharing statement

Data will be made available to the editors of the journal for review or query upon request. The datasets supporting the conclusions of this article are available from the corresponding author upon reasonable request.

Declaration of interests

M.G. has nothing to disclose. M.C. has nothing to disclose. J.T.S. has nothing to disclose. J.S. has nothing to disclose. P.V. has nothing to disclose. C.O. has nothing to disclose. M.F.C. has nothing to disclose. A.B. has nothing to disclose. M.S. has nothing to disclose.

Credit authorship contribution statement

Maria Gonçalves: statistical analyses, formal analysis, draft writing, final manuscript acceptance. Mariana Cunha: data curation, data acquisition, conceptualization, study design, supervision, formal analysis, critical review of the manuscript, final manuscript acceptance. José Teixeira da Silva: conceptualization, study design, critical review of the manuscript, final manuscript acceptance. Joaquina Silva: data curation, formal analysis, critical review of the manuscript, final manuscript acceptance. Paulo Viana: data curation, formal analysis, critical review of the manuscript, final manuscript acceptance. Cristiano Oliveira: formal analysis, critical review of the manuscript, final manuscript acceptance. Margarida F Cardoso: statistical analyses, formal analysis, final manuscript acceptance. Alberto Barros: data curation, formal analysis, critical review of the manuscript, final manuscript acceptance. Mário Sousa: project administration, funding acquisition, conceptualization, study design, supervision, formal analysis, critical review of the manuscript, final text editing, final manuscript writing, final manuscript submission, and final manuscript acceptance.

Ethics approval and consent to participate

According to the determinations of the National Law of Medically Assisted Procreation (Law of 2006) and guidelines of the National Council for Medically Assisted Procreation (CNPMA-2021), the use of patient clinical databases for diagnosis and research may be used without additional ethical approval, as long as research is used under strict individual anonymity and after informed and written consent from the patient. The use of this data by members of ICBAS was further authorized by the Ethics Committee ICBAS/CHUP with project number: 2024/CE/P23(P434/2024/CETI).

This work did not involve human or animal experiments and thus the provisions of the Declaration of Helsinki as revised in Tokyo 2004 do not apply to this work. All authors have read and agreed to the order of appearance and to the published version of the manuscript. The authors also declare that they have followed all the rules of ethical conduct regarding originality, data processing and analysis, or duplicate publication.

Capsule

In high-responders, using a GnRH-agonist as oocyte maturation trigger improves blastocyst formation, implantation, clinical pregnancy, and cumulative clinical pregnancy rates. To avoid OHSS, a freeze-all policy is suggested.

Introduction

Around 1:6 people worldwide suffer from lifetime infertility[1,2]. Assisted Reproduction Technologies (ART), such as in-vitro fertilization (IVF)[3] and intracytoplasmic sperm injection (ICSI)[4], benefited from developments in controlled ovarian stimulation (COS) protocols, either using gonadotropin-releasing hormone (GnRH) agonists[5,6] or GnRH-antagonists[6-8].

Ovarian hyperstimulation syndrome (OHSS) is the most frequent ART complication[9-11], occurring as an excessive response to COS[12]. OHSS can lead to cycle cancellation, prolonged bed rest, hospitalization, and death[13]. The main identified risk factors for OHSS are young age, low body mass index (BMI), polycystic ovary syndrome (PCOS), higher doses of exogenous gonadotropins administered, high absolute or rapidly rising serum estradiol (E2) levels, high number of developing follicles or retrieved oocytes, and previous OHSS episodes[14]. Although patients who exhibit a high-response to COS present high pregnancy rates[15,16], they also have a substantially higher risk for OHSS[17]. In this context, a consensus for the definition of high-responders[18] would be critical to avoid OHSS, while not interfering with clinical outcomes[16].

Several strategies have been implemented to lower/eliminate OHSS, such as the use of GnRH-agonists instead of human choriogonadotropin (hCG) as oocyte maturation triggers, as well as the freeze-all approach, which consists of the cryopreservation of all embryos (or oocytes) obtained in one stimulation cycle[19]. Using a GnRH-agonist to trigger the endogenous luteinizing hormone (LH)-surge in ART cycles[20] was shown to reduce the OHSS risk by inducing a quick and reversible luteolysis[20-24]. Additionally, as GnRH-agonists induce more physiological LH and follicle-stimulating hormone (FSH) surges, their use as triggers can result in better oocyte and embryo quality[25] and improve endometrial quality by lowering steroid levels at the luteal phase[26,27]. However, GnRH-agonists' effect in luteolysis also results in luteal phase deficiency, with lower estradiol and progesterone levels and shorter luteal phase duration[25,28,29]. Therefore, lower implantation and clinical pregnancy (CP) rates were reported after GnRH-agonist triggering, despite luteal phase supplementation with estradiol[25,30,31].

Few studies have been dedicated to comparing the use of hCG and GnRH-agonist triggers in women classified as high-responders, with a lack of consensus defining this population, and the amount of clinical data offered is also limited. To provide new solid information, this study evaluated a large population cohort of high-responders comparing hCG to a GnRH-agonist with hCG at oocyte pick-up day, as triggers, presenting detailed OHSS, embryological, clinical, newborn, and cumulative clinical outcomes.

Materials and Methods

Ethic guidelines and informed consent

This study was performed according to the National Law of Medically Assisted Procreation (Law n.° 32/2006, 26 July), and National Council for Medically Assisted Procreation (CNPMA, 2021) guidelines, being approved by the University Hospital's Ethics Committee (2024/CE/P23(P434/2024/CETI)). Clinical data was used under anonymity and after the patient's informed and written consent.

Study design and population

652 patients with high-responder criteria were selected from nine consecutive years (2012-2020). Infertile women <38 years old[32] were selected as high-responders under the additional presence of at least one of the following criteria: E2 levels ≥3000 pg/ml[32,33]; last ultrasound with ≥20 follicles[33-36]; or ≥13 *cumulus*-oocyte complexes (COC) retrieved[35].

Selected patients were divided according to the oocyte maturation trigger: 221 patients underwent 232 hCG embryo transfer cycles (ETC) and 431 patients underwent 473 GnRH-agonist ETC. The decision to use hCG or GnRHa as the trigger was dependent on the clinical evaluation of the patient. Data on patient demographic and stimulation characteristics and embryological, clinical, and newborn outcomes were detailly evaluated. The outcomes of the respective 534 frozen-thawed embryo transfer (FET) cycles were also analyzed, resulting in a total of 1239 evaluated cycles.

Karyotyping[37] and Y-chromosome screening[38] were executed according to general protocols. Testicular sperm extraction (TESE) or aspiration (TESA)[39] and preimplantation genetic testing (PGT)[40,41] were performed according to published protocols. Conventional semen analysis was performed according to WHO 2021 guidelines[42]. Embryological and clinical definitions followed the International Glossary on Infertility and Fertility Care[43].

Ovarian stimulation

Patients underwent COS with a GnRH-antagonist protocol (Merck Serono, Switzerland; Organon, Netherlands). For stimulation, recombinant FSH (rFSH) was used (Merck-Serono). Ovulation trigger was performed either with hCG (Organon), recombinant hCG (rhCG) (Merck-Serono), or a GnRH-agonist (Ipsen Pharma Biotech). E2, progesterone (P4), and LH serum levels were evaluated on the day or one day before trigger[44,45]. Follicles with ≥11 mm were considered suitable and were retrieved through ultrasound-guided ovarian puncture.

Gamete and embryo handling

Gamete and embryo handling were performed with media from Origio (Denmark) or Vitrolife (Sweden). COC were collected in SynVitro Flush-Medium (Origio), and left in sequential Fert-Medium (Origio) inside ESCO-incubators (Esco Medical, Singapore), until insemination or denudation. In IVF cycles, insemination was performed in Fert-Medium, and zygotes were placed in Cleavage Medium (Origio). In ICSI cycles, denudation was performed in sperm preparation medium (SPM) (Origio), under oil (Vitrolife), first enzymatically (Cumulase, Origio) and then mechanically (Handling pipettes, Vitrolife). After denudation, oocytes were left in a sequential Cleavage Medium inside ESCO-incubators. Microinjection was performed as previously described[46].

Embryos were cultured in a sequential Cleavage Medium up to day-3, and then in sequential Blast Medium (Origio), up to embryo transfer or freezing, inside an Embryoscope apparatus (Vitrolife). Embryo grading followed Istanbul Consensus guidelines[47]. Ultrasound-guided embryo transfer was performed with a Sure View Wallace Embryo Replacement Catheter or Wallace malleable stylet (Smiths Medical Int, UK).

Embryo cryopreservation

Blastocysts were kept in Embryoslide culture dishes (Vitrolife) containing Sequential Blast medium. Expanded blastocysts were submitted to Laser blastocoel collapse before freezing (Research Instruments, United Kingdom), transferred to Reproplate culture dishes (Kitazato Corp, Japan) in Equilibration solution (Kitazato Corp) for 15 min at room temperature (RT), then in Vitrification solution (Kitazato Corp) for 60 sec at RT, and finally aspirated to open cryotop straws (Kitazato Corp), being immediately plunged in liquid nitrogen.

Embryo thawing

Straws were plunged in Oosafe tissue culture dishes (SparMed, Denmark) containing Thawing Solution (TS) medium (Kitazato Corp), 1 min at 37°C, transferred to Reproplate culture dishes containing Diluent Solution (DS) medium (Kitazato Corp), 3 min at RT, then in Washing Solution (WS) medium (Kitazato Corp), 5 min at RT, washed with WS medium, 1 min, and finally placed in sequential Blast medium, under oil. Retracted or slightly expanded blastocysts were submitted to Laser assisted hatching (Research Instruments), and incubated for 2h in sequential Blast medium, under oil, inside ESCO incubators. Blastocysts were then transferred to a sequential Blast medium, without oil, followed by embryo transfer.

Luteal supplementation for fresh embryo transfer

Luteal supplementation consisted of intravaginal progesterone (LD Collins, UK; EFFIK, Portugal), 800 mg daily since the day of oocyte retrieval in hCG-triggered cycles. In GnRH-agonist trigger cycles, oral estradiol was added (Isdin, Novo Nordisk, Denmark), 2 mg 12/12h, for the same period as progesterone, and, in all cases, a single injection of rhCG (62 IU) was administered at the day of oocyte pick-up[48].

Luteal supplementation for frozen-thawed embryo transfer

Artificial cycle

The endometrium was prepared with E2 (Estrofen, Isdin), 6 mg (2 mg morning, 4 mg night) since day 2 of menses. Acetylsalicylic acid, 150 mg (Tromalyt, Rottapharm, Ireland), one per day, was added concomitantly with E2. Eleven days after, if the endometrium was ≥7 mm and there weren't follicles ≥ 12 mm, intravaginal administration of P4 (Cyclogest, LD Collins or Progeffik, EFFIK), 800 mg daily, was added. Embryo transfer was performed on day-6 after beggining of P4.

Natural modified cycle

Under ultrasound surveillance, when a preovulatory follicle was observed and the endometrium thickness was ≥7 mm, E2, LH and P4 levels were measured, and a single injection of rhCG (250 IU) was administered. Two days after the oocyte maturation trigger, micronized P4 (Cyclogest or Progeffik), 400 mg daily, was initiated. Embryo transfer was performed on day-7 after the oocyte maturation trigger.

Pregnancy confirmation

Implantation was confirmed by a rise in serum βhCG, 12 days after embryo transfer. CP was established by ultrasound at 6 weeks of gestation[43]. Progesterone/estradiol was maintained until βhCG serum assay and, if above 20 mUI/ml, continued until 10 weeks of gestation.

Primary outcomes

Primary outcomes were OHSS, CP, ongoing pregnancy (OP), livebirth delivery (LBD), newborn (NB) rates, and cumulative clinical outcomes.

Statistical analysis

Statistical analysis was carried out through the IBM SPSS Statistics 29 program for iOS. Means were compared by the t-Test for independent samples. Categorical variables were analyzed using descriptive statistics and the Chi-square test, with continuity correction. In some variables, in the presence of cells with expected n value <5 in contingency tables, the Fisher exact Test was used. All statistical tests were two-tailed.

Associations of the different outcomes with trigger (GnRHa *vs*. hCG) were investigated using logistic regression. The outcomes considered for each cycle were CP, OP, LBD and to have a newborn. As a first step, the univariable association between the trigger and each outcome was investigated. As a second step, the association of each outcome with treatment was obtained by controlling for age, AMH, and number of follicles in a multivariable model. The subsets ETC and FET were considered. The same methodology was considered for the global analysis of all treatments, GnRHa and hCG, irrespective of the number of cycles performed, considering the outcomes of having at least one CP, one OP, one LBD, and one newborn, in at least one of the cycles. The significance level considered was 0.05 ($P<.05$).

Results

652 high-responder patients performed 705 ART cycles, 232 cycles triggered with hCG (32.9%) and 473 cycles triggered with a GnRH-agonist (67.1%).

Concerning demographic data, the GnRH-agonist group showed a significantly lower mean female age, with no significant differences between groups regarding male age and time of infertility (Supplemental Table I). Concerning karyotype abnormalities (Supplemental Table II), no significant differences were observed between groups. The total rate of chromosomal abnormalities was 3.5% in males and 2.8% in females, evidencing a higher rate than in the general population (0.5-1%)[49]. There were two cases with Y-chromosome microdeletions (in AZFc), one per group, each giving birth to a healthy NB.

Concerning infertility factors, the GnRH-agonist group showed significantly lower rates of male-factor-only, with no significant differences between groups regarding female-factor-only or mixed-factors (Supplemental Table I). The GnRH-agonist group evidenced significantly higher PCOS[50] and ovulatory dysfunction cases, and significantly lower endometriosis and tubal factor cases, with no significant differences observed between groups regarding hyperprolactinemia and uterine factor cases (Supplemental Table III).

Concerning female basal characteristics (Supplemental Table I), the GnRH-agonist group evidenced significantly higher mean levels of basal LH (bLH) and anti-Müllerian hormone (AMH), and significantly lower mean BMI, with no significant differences between groups regarding the mean levels of basal FSH (bFSH). Considering the gynecological/obstetrical history, the GnRH-agonist group evidenced a significantly lower mean number of previous pregnancies and no significant differences in the number of previous ART treatment cycles.

Regarding semen parameters, no significant differences were found between groups (Supplemental Table III). Concerning sperm-origin, the GnRH-agonist group showed significantly lower use of ejaculated sperm, with no significant differences between groups regarding the use of fresh or frozen testicular sperm, frozen homologous sperm, or donor sperm.

Concerning the use of IVF or ICSI (Supplemental Table IV), although no significant differences were observed between groups regarding the use of IVF/ICSI, inside-group comparisons showed a significantly higher use of ICSI (P<.001). Concerning stimulation characteristics (Supplemental Table IV), the GnRH-agonist group evidenced a significantly higher mean number of follicles and E2 levels, and a significantly lower mean total gonadotropin dose. There were no significant differences between groups regarding endometrium thickness, time of stimulation, or P4 levels.

Regarding embryological outcomes (Table I), the GnRH-agonist group evidenced a significantly higher mean number of COC, zygotes, day-3 high-quality embryos, and day-4 embryos, and significantly higher blastocyst rates. There were no significant differences between groups in oocyte maturity, fertilization, embryo cleavage, or high-quality embryo rates. The GnRH-agonist group

presented a significantly lower mean number of transferred embryos, with no significant differences between groups regarding the day of embryo transfer, with a similar predominance of day-5 transfers.

Concerning clinical outcomes (Table II), no significant differences between groups were observed regarding the rates of OHSS and severe OHSS (with hospitalization). The GnRH-agonist group showed significantly higher rates of freeze-all cycles and a higher mean number of total frozen embryos, with no significant differences between groups regarding the rate of total FET cycles. The GnRH-agonist group evidenced significantly higher CP and implantation rates and significantly lower twin pregnancy rates. No significant differences between groups were found regarding ectopic pregnancy, abortion, OP, or LBD rates. No triplet pregnancies were recorded. Concerning cycle cancellation rates, the GnRH-agonist group evidenced significantly higher total cycle cancellation rates, cycle cancellation rates due to OHSS risk, and PGT-cycle cancellation rates. There were no significant differences between groups regarding other causes of cycle cancellation (Supplemental Table V).

OHSS developed in 25 fresh cycles (Supplemental Table VI). Of the 25 cases with OHSS, 10 (40.0%) underwent freeze-all, and 15 underwent ETC. No severe OHSS occurred under freeze-all. Of the OHSS cases with ETC, 2 did not result in a clinical pregnancy (1-hCG, 1-GnRH-agonist) and 13 did (5-hCG, 8-GnRH-agonist). Of the OHSS-pregnant cases, 7 (53.8%) did not develop severe OHSS (2-hCG, 5-GnRH-agonist) and 6 (46.2%) developed severe OHSS (3-hCG, 3-GnRH-agonist). All the patients who developed severe OHSS were clinically pregnant.

Concerning NB outcomes (Table III), no significant differences between groups were observed in NB rates and sex ratios. No NB malformations were recorded. There were no significant differences between groups regarding the mean gestational age. The GnRH-agonist group showed a significantly higher very-pre-term mean gestational age. No other significant differences were found. Regarding NB birthweight, the GnRH-agonist group evidenced a significantly higher total mean birthweight and normal-weight rate, and lower rates of low-weight cases. No other significant differences were observed.

Concerning FET cycles (Table IV), no significant differences were noticed between groups regarding the CP, implantation, abortion, OP, LBD, and NB rates, or in the mean gestational age and NB birthweight. The GnRH-agonist group evidenced significantly lower twin pregnancy rates. There were neither ectopic pregnancies nor NB malformations. A stillbirth occurred in the GnRH-agonist group. Regarding cumulative outcomes (ETC and FET, per cycle), the GnRH-agonist group showed significantly higher cumulative CP rates. No significant differences between groups were observed for cumulative OP, LBD, and NB rates. Concerning FET cancellation rates, no significant differences between groups were observed (Supplemental Table VII).

The outcomes from fresh ETC and FET cycles were compared (Supplemental Table VIII). In the GnRH-agonist group, the CP, OP, LBD, and NB rates were significantly higher in the fresh ETC subgroup. In the hCG group, the NB rate was significantly higher in the fresh ETC subgroup, with no significant differences regarding CP, OP, or LBD rates.

FET cycles were divided into a freeze-all FET subgroup and a surplus embryos FET subgroup (cycles with surplus embryos that were cryopreserved), and compared per trigger protocol (Supplemental Tables IX and X). No significant differences were observed regarding the CP, OP, LBD, and NB rates in any of these comparisons.

To evaluate the effect of possible confounding factors, selected variables were studied: type of ART, PCOS and PGT (Supplemental Table XI), karyotype abnormalities (Supplemental Table XII), and sperm-origin (Supplemental Tables XIII and XIV). There were no significant differences between groups regarding CP, OP, LBD, and NB rates, with two exceptions: compared to fresh-ejaculated sperm, the GnRH-agonist group showed significantly lower NB rates in TESA cases (and, globally, there were significant differences in CP, OP, and NB rates), and lower OP and LBD rates in donor sperm cases (Supplemental Table XIV).

The female high-responder population was further analyzed regarding the presence of two or more inclusion criteria. The GnRH-agonist group presented significantly ($p<.001$) higher rates of cases with the four criteria age/E2/follicles/COC (1.5% *vs.* 10.5%), the three criteria age/follicles/COC (22% *vs.* 36.9%), and the two criteria age/follicles (8.3% *vs.* 32%); and significantly lower rates of cases with the two criteria age/COC (29.8% *vs.* 10.1%) and age/estradiol (35.1% *vs.* 4.3%). No significant differences were found in the rate of cases with the three criteria age/estradiol/follicles (1.0% *vs.* 3.6%) and age/estradiol/COC (2.4% *vs.* 2.6%).

The GnRH-agonist group evidenced a significantly lower female age, higher AMH levels, and a higher mean number of follicles. As these factors are associated with a higher hyperstimulation risk, a multivariable logistic regression analysis was performed, controlling those factors. After adjusting, results showed no significant differences between groups regarding the likelihood of achieving CP, OP, LBD, or of having a newborn (Supplemental Table XV).

The outcome "to have at least one CP per initiated cycle" in at least one of the fresh or respective FET cycles was considered (Supplemental Table XV). After univariable logistic regression, CP was significantly more likely with GnRHa than with hCG. However, after multivariable logistic regression, there were no significant differences. Both univariable and multivariable logistic regressions found no significant differences between groups concerning OP, LBD, and the outcome of having a newborn in total cycles (ETC and FET).

Discussion

ART treatments with personalized COS protocols aim to obtain a sufficient number of mature competent oocytes, avoid OHSS, and achieve a healthy child. Success depends on a correct identification of ovarian good-responders, poor-responders and high-responders[16,51], especially of high-responders due to a greater OHSS risk[18].

To our knowledge, this is the largest report comparing hCG and a GnRH-agonist, with luteal hCG, as triggers in high-responder patients, with presentation of OHSS rates, and detailed data on embryologic, clinical and NB outcomes, including cumulative rates, with a similar distribution of cases.

In the absence of a consensus for defining high-responders[18], literature indications were merged[27,32,33,35] and selected our population based on four criteria (age, number of follicles, E2 levels, and retrieved COC). Other variables associated with OHSS[14] were independently evaluated.

In unselected populations, previous reports indicated that GnRH-agonist triggers were associated with reduced OHSS rates and similar clinical outcomes to hCG triggers[51,52]. Although not fully abolished with a GnRH-agonist trigger, as previously foreseen[34,36,51,53], the present results evidenced low OHSS rates (3.9% hCG *vs.* 3.4% GnRH-agonist). In the literature, the OHSS rates appear highly variable: 1.5-37.6% hCG *vs.* 0.0-16.1% GnRH-agonist[51,54-64].

Freeze-all effectively prevents severe OHSS[19,65-67]. In the present results, the GnRH-agonist trigger was associated with significantly higher rates of freeze-all cycles and embryo transfer cancellation due to OHSS risk, with no severe OHSS occurring under freeze-all. This could be expected, as pregnancy hCG elevation is a risk factor for OHSS[68]. Data thus suggests that, in high-responders, despite the use of a GnRH-agonist trigger, only freeze-all avoids severe OHSS, nevertheless, reaching high CP, OP, LBD, and NB rates after FET.

Although previously stated that embryological outcomes were similar with both triggers[58,64,69], the present results showed that, with a GnRH-agonist trigger, a higher mean number of COC, fertilized oocytes, and high-quality embryos, and a higher blastocyst rate are obtained. A higher mean number of COC, mature oocytes, zygotes, and blastocysts with this trigger was also previously described[62].

The use of a GnRH-agonist trigger obliges a special luteal phase support in fresh ETC. Previous studies, in high-responders, suggest that using a GnRH-agonist in luteal support is associated with OHSS absence, with similar implantation, CP, and OP rates to the ones observed with hCG triggering[57]. Other authors suggested luteal supplementation with estradiol and hCG in GnRHa triggered cycles[48,69], obtaining similar clinical outcomes as with hCG triggering, however, they could not fully abolish severe OHSS, except for one report[48,51,55,56,58,59]. Another report with a GnRH-agonist trigger showed higher implantation, LBD, and embryo euploidy rates in comparison to hCG triggers[62]. In the present report, where a single hCG injection was administered at oocyte pick-up

day, GnRH-agonist trigger cycles presented significantly higher implantation and CP rates, with no significant differences between trigger groups in the abortion, ectopic pregnancy, OP, LBD, and NB rates. High clinical outcome rates in GnRH-trigger cycles have been attributed to the simultaneous surge of FSH and LH, which enables a better oocyte quality[69,70], and to the influence of the hCG bolus and E2 in the luteal support, which counteracts the negative impact of premature luteolysis[48,69]. However, the present multivariate analysis, considering three important factors - female age, AMH levels, and mean number of follicles - revealed no significant differences between groups after adjusting.

In the present report, the higher rate of twin pregnancies in the hCG trigger group may be justified by the higher number of transferred embryos in this group. No differences between trigger groups were found concerning mean gestational age. Concerning birthweight, it had been suggested that higher E2 levels could cause lower birthweight in cycles triggered with a GnRH-agonist[63]. Contrarily, the present results evidenced that cycles with a GnRH-agonist trigger were associated with higher mean birthweight and higher rates of normal birthweight. In a previous study of unselected patients, a positive association between GnRH-agonist triggering and NB malformations was recorded[36], which was not verified in the present population, with no NB malformations observed.

The impact of FET is yet unclear, as lower CP rates[71] and higher abortion rates[72] have been observed in FET cycles, whereas other studies found no detrimental impact[73]. In the present populations, between-group comparisons regarding FET cycles revealed no significant differences. Concerning inside-group comparisons, the GnRH-agonist trigger group evidenced significantly higher CP, OP, LBD, and NB rates in fresh ETC compared to FET cycles, whereas on cycles with hCG-trigger, similar rates were observed in fresh ETC and FET cycles, except for NB rates, which were higher in fresh cycles.

It was proposed that the higher number of frozen embryos in GnRH-agonist trigger cycles could condition higher cumulative CP rates[63]. The present results showed a significantly higher mean number of frozen embryos and higher cumulative CP rates in the GnRH-agonist trigger group, with no significant differences observed between groups regarding OP, LBD, and NB cumulative rates. Another factor that could interfere with this higher cumulative CP rate is that, in the GnRH-agonist group, there was a higher CP rate per fresh ETC. Although the same phenomenon was similarly observed, after univariable logistic regression analysis, with the outcome "to have at least one CP per initiated cycle", after multivariable logistic regression analysis no significant differences were found. Nevertheless, it was possible to obtain high CP, LBD, and NB rates with FET cycles, which is an excellent indicator for this population.

Other reports, in high-responders, presented dispersed and conflicting clinical findings. Some found similar CP rates[51,53,55-57,59,62,64,65], higher CP rates with a GnRH-agonist[58], similar LBD rates[55,56,59,63,64], or higher LBD rates, including cumulative LBD rates[61,62]. Better comparisons are jeopardized by the absence of a standardized high-responder definition, with criteria varying considerably. Additionally, comparisons are frequently hampered by the lack of, or different evaluations of embryological, clinical, and NB indicators[34,51,53,54,56,57,58-61].

Conclusions

This study presents a large patient series with well-defined criteria for high-responders critically taken from the literature. The factor age was fixed, and 3 more criteria were added, achieving the use of 3 to 4 criteria in about 45% of the cases, mainly in the GnRH-agonist trigger group (about 54%). This means that, in about half the cases, only 2 criteria were met. Prospective studies are thus necessary, with fixed criteria. For this, it is important to standardize the high-responder definition[74], as previously occurred with poor-responders[75]. The most optimal protocol for high-responders should have an acceptable rate of cancellation, maximal pregnancy and livebirth rates, and absence of OHSS[76]. Bearing this in mind, although not abolishing OHSS, it was observed that the use of a GnRH-agonist as a trigger in high-responders was associated with higher blastocyst formation, implantation, clinical pregnancy, and cumulative clinical pregnancy rates. However, multivariable logistic regression analysis revealed no significant differences. Therefore, additionally, to abolish OHSS, data suggests the need for a sole consensus criterion to select the oocyte maturation trigger, and that freeze-all should be applied to all suspected OHSS cases, with the reassurance that, after FET cycles, very high clinical outcomes are obtained.

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Appendix

TABLE I Embryological outcomes in fresh embryo transfer cycles

Parameters	hCG	GnRHa	Total	P
Patients (n)	221	431	652	
Cycles (n)	232	473	705	
Embryo transfer cycles (n)	208	327	535	
Embryological outcomes				
COC (mean, std, range)	13.1 ± 4.7 (2-40)	14.0 ± 5.1 (1-54)	13.7 ± 5.0 (1-54)	**.020**
MII (mean, std, range)	10.4 ± 4.1 (1-34)	10.9 ± 4.4 (1-31)	10.7 ± 4.3 (1-34)	.132
Maturation rate (rate)	79.0	77.6	78.1	.136
Zygotes (mean, std, range)	7.5 ± 3.6 (1-19)	8.1 ± 3.7 (1-23)	7.9 ± 3.7 (1-23)	**.040**
Fertilization rate (mean, std, range)	72.2	73.4	73.0	.279
Embryos cleaved at day 2 (mean, std, range)	7.3 ± 3.5 (1-19)	7.8 ± 3.7 (1-22)	7.6 ± 3.6 (1-22)	.095
Embryo cleavage rate (rate)	95.6	95.5	95.5	.805
Day 3 embryos (mean, std, range)	6.4 ± 3.2 (1-18)	6.9 ± 3.5 (1-21)	6.7 ± 3.4 (1-21)	.068
Day 3 grade A/B embryos (mean, std, range)	6.2 ± 3.1 (1-18)	6.8 ± 3.5 (1-21)	6.6 ± 3.4 (1-21)	**.044**
Day 3 grade A/B rate (AB/d3) (rate)	96.6	97.3	97.1	.166
Day-4 embryos (mean, std, range)	5.2 ± 2.9 (1-17)	5.7 ± 3.2 (1-20)	5.6 ± 3.2 (1-20)	.058
Day-5 embryos (mean, std, range)	4.4 ± 2.6 (1-14)	4.9 ± 2.9 (1-20)	4.8 ± 2.8 (1-20)	.062
Blastocyst rate (rate)	51.6	56.0	54.6	**.003**
No. of transferred embryos (mean, std, range)	1.6 ± 0.5 (1-2)	1.3 ± 0.5 (1-2)	1.4 ± 0.5 (1-2)	**<.001**
Single embryo transfer (rate)	43.3	69.4	59.3	**<.001**
Double embryo transfer (rate)	56.7	30.6	40.7	**<.001**
Embryo transfer at day 2 (/ETC) (rate)	4.8	2.1	3.2	.086
Embryo transfer at day 3 (/ETC) (rate)	5.8	6.1	6.0	.869
Embryo transfer at day 4 (/ETC) (rate)	5.3	3.4	4.1	.274
Embryo transfer at day 5 (/ETC) (rate)	83.2	86.2	85.0	.332

Note: Significant differences between groups using human choriogonadotropin (hCG) or gonadotropin-releasing hormone agonist (GnRHa) as oocyte maturation trigger. Significance at P<.05.

ETC = embryo transfer cycles; COC = cumulus-oocyte complexes (aspirated oocytes); MII = metaphase-II oocytes (mature oocytes); Zygotes = normal fertilized oocytes exhibiting 2 polar bodies and two pronuclei; Embryo grade A/B = high-quality embryos.

TABLE II Clinical outcomes in fresh embryo transfer cycles

Parameters	**hCG**	**GnRHa**	**Total**	**P**
Patients (n)	221	431	652	
Cycles (n)	232	473	705	
Embryo transfer cycles (n)	208	327	535	
Stimulation outcomes				
OHSS (/cycle) (rate)	3.9	3.4	3.5	.738
OHSS with hospitalization (/cycle) (rate)	1.3	0.6	0.9	.371
OHSS without hospitalization (/cycle) (rate)	2.6	2.7	2.7	.935
OHSS with hospitalization (/OHSS) (rate)	33.3	18.8	24.0	.412
OHSS without hospitalization (/OHSS) (rate)	66.7	81.2	76.0	.412
Freeze-all cycles (/cycle) (rate)	6.0	27.5	20.4	**<.001**
Total embryo cryopreservation cycles (/cycle) (rate)	50.4	48.0	48.8	.543
Total No. cryopreserved embryos (/cycle) (mean, std, range)	2.1 ± 2.7 (0-15)	3.1 ± 3.0 (0-15)	2.8 ± 2.9 (0-15)	**<.001**
Pregnancy outcomes				
BP (/ETC) (rate)	5.3	4.9	5.0	.839
CP (/ETC) (rate)	51.9	60.9	57.4	**.042**
Sacs (n)	136	214	350	
Implantation rate (rate)	41.7	50.2	45.5	**.020**
Singletons (/CP) (rate)	70.4	87.9	81.8	**<.001**
Twins (/CP) (rate)	28.7	10.6	16.9	**<.001**
Ectopic pregnancy (/CP) (rate)	0.9	1.5	1.3	1.000
Abortion (/CP) (rate)	15.7	18.1	17.3	.603
OP (/ETC) (rate)	43.3	48.9	46.7	.201
Delivery (/ETC) (rate)	43.3	48.9	46.7	.201
Eutocic delivery (/Delivery) (rate)	35.6	47.5	43.2	.067
Dystocic delivery (/Delivery) (rate)	64.4	52.5	56.8	.067
Stillbirth (rate)	1.1	0	0.4	
LBD (/ETC) (rate)	42.8	48.9	46.5	.165

Note: Significant differences between groups using human choriogonadotropin (hCG) or gonadotropin-releasing hormone agonist (GnRHa) as oocyte maturation trigger. Significance at P<.05.

OHSS = ovarian hyperstimulation syndrome; ETC = embryo transfer cycles; BP = biochemical pregnancy; CP = clinical pregnancy; OP = ongoing pregnancy; Delivery = eutocic+dystocic; LBD = live birth delivery (delivery-stillbirth).

TABLE III Newborn outcomes in fresh embryo transfer cycles

Parameters	**hCG**	**GnRHa**	**Total**	**P**
Patients (n)	221	431	652	
Cycles (n)	232	473	705	
Embryo transfer cycles (n)	208	327	535	
Newborn outcomes				
Newborn (/ETC) (rate)	53.8	53.5	53.6	.941
Male (/NB) (rate)	47.3	54.3	51.6	.249
Female (/NB) (rate)	52.7	45.7	48.4	.249
Male/Female ratio	0.90	1.19	1.06	
Female/Male ratio	1.11	0.84	0.95	
NB malformations (/NB) (n)	0	0	0	
Gestational age (weeks) (mean, std, range)	37.6 ± 3.2 (22-41)	38.2 ± 2.0 (29-41)	38.0 ± 2.5 (22-41)	.058
Term (mean, std, range, rate)	38.7 ± 1.1 (37-41) 78.9	38.8 ± 1.1 (37-41) 86.2	38.8 ± 1.1 (37-41) 83.5	.713 .137
Preterm (mean, std, range, rate)	33.2 ± 4.4 (22-36) 21.1	34.4 ± 1.9 (29-36) 13.8	33.9 ± 3.3 (22-36) 16.5	.257 .137
Very PT (mean, std, range, rate)	23.7 ± 2.1 (22-26) 3.3	29.5 ± 0.7 (29-30) 1.3	26.0 ± 3.5 (29-30) 0.8	**.035** .355
Extremely PT (mean, std, range, rate)	23.7 ± 2.1 (22-26) 3.3	0	23.7 ± 2.1 (22-26) 1.2	
NB Weight (g) (mean, std, range)	2739.0 ± 622.6 (560-4250)	2924.3 ± 601.7 (325-4320)	2852 ± 615.5 (325-4320)	**.013**
Overweight (mean, std, range, rate)	4165.0 ±120.2 (4080-4250) 1.8	4212.5 ± 108.7 (4080-4320) 2.3	4196.7 ± 102.9 (408-4320) 2.1	.649 1.000
Normal weight (mean, std, range, rate)	3024.8 ± 325.8 (2500-3910) 67.3	3102.8 ± 341.5 (2500-3950) 80.6	3076.0 ± 337.5 (2500-4250) 75.4	.107 **.011**
Low weight (mean, std, range, rate)	2033.0 ± 474.5 (560-2460) 30.9	2011.3 ± 364.7 (1259-2450) 17.1	2022.9 ± 423.4 (560-2460) 22.5	.840 **.007**
Very LW (mean, std, range, rate)	977.3 ± 405.5 (560-1349) 3.6	1378.0 ± 105.7 (1250-1495) 2.9	1199.9 ± 334.5 (560-1495) 3.2	.068 .738
Extremely LW (mean, std, range, rate)	630.0 ± 99.0 (560-700) 1.8	0	630.0 ± 99.0 (560-700) 0.7	

Note: Significant differences between groups using human choriogonadotropin (hCG) or gonadotropin-releasing hormone agonist (GnRHa) as oocyte maturation trigger. Significance at P<.05.

ETC = embryo transfer cycles; NB = newborn; PT = preterm; LW = low weight.

TABLE IV Frozen-thawed embryo transfer cycles' outcomes and cumulative outcomes

Frozen-thawed embryo transfer outcomes				
Parameters	**hCG**	**GnRHa**	**Total**	**P**
Patients (n)	221	431	652	
Cycles (n)	232	473	705	
Embryo transfer cycles (n)	208	327	535	
FET cycles (n)	127	407	534	
Outcomes				
BP (/FET) (rate)	4.7	7.6	6.9	.262
CP (/FET) (rate)	41.7	46.9	45.7	.305
Sacs (n)	66	210	276	
Implantation rate (rate)	52.0	51.6	51.7	.942
Singletons (/CP) (rate)	73.6	90.6	86.9	**<.001**
Twins (/CP) (rate)	26.4	9.4	13.1	**<.001**
Ectopic pregnancy (/CP) (rate)	0	0	0	
Abortion (/CP) (rate)	15.1	23.0	21.3	.212
OP (/FET) (rate)	35.4	35.9	35.8	.928
Delivery (/FET) (rate)	35.4	35.6	35.6	.968
Eutocic delivery (/Delivery) (rate)	33.3	29.7	30.5	.640
Dystocic delivery (/Delivery) (rate)	66.7	70.3	35.6	.640
Stillbirth (rate)	0	0.2	0.2	
LBD (/FET) (rate)	35.4	35.4	35.4	.991
Newborn (/FET) (rate)	40.9	38.6	39.1	.633
Gestational age (weeks) (mean, std, range)	37.5 ± 2.2 (28-41)	37.6 ± 2.4 (26-42)	37.6 ± 2.4 (26-42)	.722
NB Weight (g) (mean, std, range)	3046.6 ± 526.7 (1870-4050)	3078.2 ± 634.9 (700-4100)	3070.4 ± 608.8 (700-4100)	.749
Cumulative outcomes				
Outcomes	**hCG**	**GnRHa**	**Total**	**P**
CP (/cycle) (rate)	69.4	82.5	78.2	**<.001**
OP (/cycle) (rate)	58.2	64.7	62.6	.094
LBD (/cycle) (rate)	57.8	64.3	62.1	.094
Newborn (/cycle) (rate)	70.7	70.2	70.4	.891

Note: Significant differences between groups using human choriogonadotropin (hCG) or gonadotropin-releasing hormone agonist (GnRHa) as oocyte maturation trigger. Significance at P<.05.
ETC = embryo transfer cycles; FET = frozen-thawed embryo transfer cycles; BP: biochemical pregnancy; CP = clinical pregnancy; OP = ongoing pregnancy; LBD = live birth delivery; NB = newborn.

SUPPLEMENTAL TABLE I Demographic data of patients

Parameters	hCG	GnRHa	Total	P
Patients (n)	221	431	652	
Cycles (n)	232	473	705	
Male age (years) (mean, std, range)	36.4 ± 5.3 (28-64)	35.7 ± 4.5 (24-55)	35.9 ± 4.7 (24-64)	.077
Female age (years) (mean, std, range)	33.3 ± 2.8 (25-37)	32.6 ± 3.0 (21-37)	32.8 ± 3.0 (21-37)	**.004**
Time infertility (years) (mean, std, range)	2.8 ± 2.2 (1-12)	3.0 ± 2.3 (1-17)	2.9 ± 2.2 (1-17)	.415
Karyotypes				
Male karyotype (normal) (rate)	97.1	95.8	96.3	.418
Female karyotype (normal) (rate)	97.2	97.1	97.1	.950
Infertility factors				
Male factor only (rate)	45.2	36.4	39.4	**.029**
Female factor only (rate)	16.7	18.1	17.6	.667
Mixed factors (rate)	30.3	36.7	34.5	.107
Female basal characteristics				
Female bFSH (mean, std, range)	6.6 ± 2.0 (0.3-16.0)	6.5 ± 2.0 (0.6-20.0)	6.5 ± 2.0 (0.3-20.0)	.781
Female bLH (mean, std, range)	5.7 ± 2.7 (0.1-24)	6.9 ± 5.7 (0.1-56.7)	6.5 ± 5.0 (0.1-56.7)	**.003**
Female AMH (mean, std, range)	4.4 ± 5.5 (0.6-47.8)	6.4 ± 7.7 (0.3-80.1)	5.9 ± 7.2 (0.3-80.1)	**.001**
Female BMI (mean, std, range)	23.0 ± 4.0 (14.7-43.1)	22.3 ± 3.3 (15.8-33.8)	22.5+-3.6 (14.7-43.1)	**.021**
G/O history				
Previous ART cycles (mean, std, range)	1.8 ± 2.0 (0-11)	1.9 ± 2.3 (0-19)	1.9 ± 2.2 (0-19)	.351
Previous pregnancies (mean, std, range)	0.6 ± 0.8 (0-5)	0.4 ± 0.7 (0-5)	0.4 ± 0.8 (0-5)	**.002**

Note: Significant differences between groups using human choriogonadotropin (hCG) or gonadotropin-releasing hormone agonist (GnRHa) as oocyte maturation trigger. Significance at P<.05.

bFSH = basal Follicle stimulating hormone (mIU/ml); bLH = basal Luteinizing hormone (mIU/ml); AMH = anti-Müllerian hormone (ng/ml); BMI = Body mass index (kg/m^2); G/O = Gynecology and Obstetrics; ART = assisted reproductive technologies.

SUPPLEMENTAL TABLE II Abnormal karyotypes

hCG			GnRHa		
Male		Female	Male		Female
karyotype	Sperm origin	karyotype	karyotype	Sperm origin	karyotype
46XY, inv(4)(p12;q11.1)	T	45X; 46XX	47XXY[1]/46XY[25]	T	46XX, t(4;13) (p15.2;q21.2)
46XY, inv(1)(q21;q32)	T	46X, t(X;3)(q2t;q26.2)	46X, inv(Y)(q)	E	46XX, inv(11) (p15.2;q23.3)
46XY/47XXY	E	45X[2]/47XXX[2]/46XX[26]	45XY, t(13q;14q)	D	46XX, inv(7) (p15.3;q11.23)
47XXY[3]/46XY[27]	E	45XX, rob(13;14)	45X[4]/46.XY[26]	T	45X[4]/46XX[54]
47XXY	T	47XXX[2]/46XX [56]	46XY, t(1;22)(p13.3;p12)	D	45X[3]/46XX[55]
47XXY	D	46XX,t(7;12) (q22;q24.32)	46XY, t(4;13)(p14;q22)	H	46XX, inv(10) (p11.2;q21.2)
			45XY, rob(13;14) (q10;q10)pat	E	45X[3]/46XX[27]
			47XXY	E	46XX, t(2;7)(p15;q22)
			47XXY	E	46XX, t(1;13) (q25.3;q12.3)
			47XXY	E	46XX, t(1;7) (p31.2;p15.1)
			47XXY	T	45X[4]/46XX[26]
			47XXY	T	46XX, t(4;6) (q21.2;p24)
			47XXY	T	
			47XXY	D	
			47XXY	D	
			47XXY	D	
			47XXY	D	
(n=6)		(n=6)	(n=17)		(n=12)

Note: abnormal female and male karyotypes in groups using human choriogonadotropin (hCG) or gonadotropin-releasing hormone agonist (GnRHa) as oocyte maturation trigger.

E = fresh ejaculated sperm; H = frozen homologous ejaculated sperm; D = donor sperm; T = testicular sperm

SUPPLEMENTAL TABLE III Infertility factors

Female infertility factors	**hCG**	**GnRHa**	**Total**	**P**
Patients (n)	221	431	652	
Hyperprolactinemia (rate)	0.0	0.8	0.6	1.000
Endometriosis (rate)	23.1	8.5	12.9	**<.001**
Ovulatory dysfunction (rate)	55.8	77.1	70.6	**<.001**
PCOS (rate)	27.9	55.5	47.1	**<.001**
Uterine factor (rate)	17.3	12.7	14.1	.262
Tubal factor (rate)	24.0	14.4	17.4	**.031**
Semen parameters	**hCG**	**GnRHa**	**Total**	**P**
TSC (mean, std, range)	157.3 ± 203.5 (0-922.5)	162.7 ± 192.3 (0-907.1)	161.0 ± 95.2 (0-922.5)	.750
TM (mean, std, range)	50.2 ± 23.1 (0-89)	51.5 ± 24.2 (0-100)	51.1 ± 23.8 (0-100)	.518
PM (mean, std, range)	36.4 ± 20.5 (0-85)	37.7 ± 21.0 (0-100)	37.2 ± 20.8 (0-100)	.472
NM (mean, std, range)	3.7 ± 4.3 (0-41)	3.5 ± 4.2 (0-40.7)	3.6 ± 4.2 (0-41)	.651
Sperm origin	**hCG**	**GnRHa**	**Total**	**P**
Ejaculated (rate)	84.9	77.8	80.1	**.026**
Testicle (rate)	11.2	15.6	14.2	.113
TESE (rate)	6.5	6.6	6.5	.964
TESE-cryo (rate)	0.4	2.1	1.6	.113
TESA (rate)	3.4	7.0	5.8	.055
Frozen homologous sperm (rate)	1.3	1.1	1.1	.722
Donor sperm (rate)	2.2	4.9	4.0	.084

Note: Significant differences between groups using human choriogonadotropin (hCG) or gonadotropin-releasing hormone agonist (GnRHa) as oocyte maturation trigger. Significance at P<.05.

PCOS = polycystic ovarian syndrome; TSC = total sperm count (10^6 per ejaculate); TM = sperm total motility (%); PM = sperm progressive motility (%); NM = sperm normal morphology (%); TESE = testicular sperm extraction (fresh sperm); TESE-cryo = testicular sperm extraction (frozen sperm); TESA = testicular sperm aspiration (fresh sperm)

SUPPLEMENTAL TABLE IV Stimulation characteristics

	hCG	GnRHa	Total	P
Parameters				
Patients (n)	221	431	652	
Cycles (n)	232	473	705	
Technique				
IVF (rate)	33.6	29.2	30.6	.229
ICSI (rate)	66.4	70.8	69.4	.229
Stimulation				
Follicles (mean, std, range)	19.7 ± 5.8 (9-40)	23.9 ± 6.5 (8-62)	22.5 ± 6.5 (8-62)	**<.001**
Endometrium (mean, std, range)	10.2 ± 1.7 (5-15)	10.1 ± 1.6 (4-16)	10.2 ± 1.6 (4-16)	.289
Gonadotropin stimulation				
Total dose (mean, std, range)	2668.1 ± 1294.8 (600-7950)	1460.1 ± 699.2 (150-5025)	1591.7 ± 834.2 (150-7950)	**<.001**
Time stimulation (mean, std, range)	8.8 ± 1.7 (1-15)	8.6 ± 1.4 (1-17)	8.6 ± 1.5 (1-17)	.077
Estradiol (mean, std, range)	1951.7 ± 897.2 (237.3-4960.0)	2279.0 ± 1285.6 (192.3-10960)	2178.7 ± 1189.1 (192.3-10960)	**<.001**
Progesterone (mean, std, range)	0.94 ± 0.88 (0.34-9.10)	0.92 ± 0.38 (0.25-2.68)	0.92 ± 0.53 (0.25-9.10)	.639
Ovulation trigger				
hCG dose (mean, std, range)	9080.5 ± 1910.6 (5000-10000)			
rhCG dose (mean, std, range)	251.7 ± 20.8 (250-500)			
GnRH agonist dose (mean, std, range)		0.2 ± 0.0 (0.2-0.2)		

Note: Significant differences between groups using human choriogonadotropin (hCG) or gonadotropin-releasing hormone agonist (GnRHa) as oocyte maturation trigger. Significance at P<.05.

IVF = in vitro fertilization; ICSI = intracytoplasmic sperm injection; Endometrium = endometrium thickness (mm); Total dose = total gonadotropin dose (IU/ml); Time stimulation (days); Estradiol (pg/ml); Progesterone (ng/ml); hCG dose = human choriogonadotropin (IU/ml); rhCG dose = recombinant human choriogonadotropin (250 µg comparable to 5000 IU hCG); Agonist dose = gonadotropin-releasing hormone agonist (0.2 mg).

SUPPLEMENTAL TABLE V Fresh embryo transfer canceled cycles - motives

Parameters	hCG	GnRHa	Total	P
Patients (n)	221	431	652	
Cycles (n)	232	473	705	
Embryo transfer cycles (ETC) (n)	208	327	535	
Cancelled cycles (rate)	10.3	30.9	24.1	**<.001**
Cancelled due to risk of OHSS (rate)	5.9	20.7	15.6	**<.001**
Cancelled due to PGT (rate)	1.3	5.7	4.3	**.006**
Cancelled due to lack of embryo development (rate)	1.7	1.7	1.7	1.000
Cancelled due to lack of normal fertilization (rate)	0.4	1.3	0.9	.436
Cancelled due to elevated progesterone levels (rate)	0.9	0.2	0.4	.212
Cancelled due to liquid in the uterine cavity (rate)	0.4	0	0.1	
Cancelled due to lack of mature oocytes (rate)	0.4	0.2	0.3	
Cancelled due to lack of sperm (rate)	0	0.2	0.1	
Cancelled due to poor endometrial quality (rate)	0	0.2	0.1	
Cancelled due to menses after punction (rate)	0	0.2	0.1	
Not otherwise specified (rate)	0	0.4	0.3	

Note: Significant differences between groups using human choriogonadotropin (hCG) or gonadotropin-releasing hormone agonist (GnRHa) as oocyte maturation trigger. Significance at P<.05.

ETC = embryo transfer cycles; OHSS = ovarian hyperstimulation syndrome; PGT = preimplantation genetic testing.

SUPPLEMENTAL TABLE VI OHSS relationship with freeze-all and clinical pregnancy

hCG			
	Without hospitalization	With hospitalization	Total
Total (n, rate)	6 (66.7)	3 (33.3)	9
With freeze-all (n, rate)	3 (100)	0 (0)	3
With clinical pregnancy (n, rate)	2 (40.0)	3 (60.0)	5
Without clinical pregnancy (n, rate)	4 (100)	0 (0)	4
GnRHa			
	Without hospitalization	With hospitalization	Total
Total (n, rate)	13 (81.2)	3 (18.8)	16
With freeze-all (n, rate)	7 (100)	0 (0)	7
With clinical pregnancy (n, rate)	5 (62.5)	3 (37.5)	8
Without clinical pregnancy (n, rate)	8 (100)	0 (0)	8
Total			
	Without hospitalization	With hospitalization	Total
Total (n, rate)	19 (76.0)	6 (24.0)	25
With freeze-all (n, rate)	10 (100)	0 (0)	10
With clinical pregnancy (n, rate)	7 (53.8)	6 (46.2)	13
Without clinical pregnancy (n, rate)	12 (100)	0 (0)	12

Note: Significant differences between groups using human choriogonadotropin (hCG) or gonadotropin-releasing hormone agonist (GnRHa) as oocyte maturation trigger.
OHSS = ovarian hyperstimulation syndrome.

SUPPLEMENTAL TABLE VII Frozen-thawed embryo transfer canceled cycles - motives

Parameters	hCG	GnRHa	Total	P
Initiated FET (n)	140	478	618	
Cancelled FET (n)	9.3	14.9	13.6	.091
Patients (n)	9	49	58	
Ongoing FET (rate)	90.7	85.1	86.4	.091
Cancelled due to early ovulation (rate)	30.8	16.9	19.0	.260
Cancelled due to liquid in the uterine cavity (rate)	15.4	2.8	4.8	.050
Cancelled due to poor response (rate)	23.1	18.3	19.0	.706
Cancelled due to embryo-endometrial asynchrony (rate)	7.7	8.5	8.3	1.000
Cancelled due to poor endometrial quality (rate)	7.7	8.5	8.3	1.000
Cancelled due to all embryos degenerated (rate)	7.7	8.5	8.3	1.000
Cancelled due to partner reasons (rate)	15.4	0	2.4	
Cancelled due to medical disease (rate)	0	12.7	10.7	
Cancelled due to anovulation (rate)	0	9.0	8.3	
Cancelled due to metrorrhagia (rate)	0	7.0	6.0	
Cancelled due to uterine polyp (rate)	0	1.4	1.2	
Cancelled due to professional reasons (rate)	0	1.4	1.2	
Cancelled due to patient medication error (rate)	0	1.4	1.2	

Note: Significant differences between groups using human choriogonadotropin (hCG) or gonadotropin-releasing hormone agonist (GnRHa) as oocyte maturation trigger. Significance at P<.05.
FET = frozen-thawed embryo transfer cycles.

SUPPLEMENTAL TABLE VIII Outcomes of fresh embryo transfer *vs.* frozen-thawed embryo transfer

Parameters	**hCG**			**GnRHa**			**Total**		
Patients (n)	221			431			652		
Cycles (n)	232			473			705		
Embryo transfer cycles (n)	208			327			535		
Initiated total FET cycles (n)		140			478			618	
Cancelled total FET cycles (n)		13			71			84	
Total FET cycles with ET (patients/cycles) (n)		78 127			239 407			317 534	
FET cycles with surplus embryos (patients/cycles) (n)		66 107			129 195			195 302	
FET cycles with freeze-all embryos (patients/cycles) (n)		12 20			110 212			122 232	
	Total Fresh ET (/ETC)	**Total FET** (/FET)	**P**	**Total Fresh ET** (/ETC)	**Total FET** (/FET)	**P**	**Total Fresh ET** (/ETC)	**Total FET** (/FET)	**P**
CP (rate)	51.9	41.7	.070	60.9	46.9	**<.001**	57.4	45.7	**<.001**
OP (rate)	43.3	35.4	.156	48.9	35.9	**<.001**	46.7	35.8	**<.001**
LBD (rate)	42.8	35.4	.182	48.9	35.6	**<.001**	46.5	35.6	**<.001**
Newborn (rate)	53.8	40.9	**.022**	53.5	38.6	**<.001**	53.6	39.1	**<.001**

Note: Significant differences between groups using human choriogonadotropin (hCG) or gonadotropin-releasing hormone agonist (GnRHa) as oocyte maturation trigger. Significance at P<.05.

ETC = embryo transfer cycles; FET = frozen-thawed embryo transfer cycles; ET = embryo transfer; CP = clinical pregnancy; OP = ongoing pregnancy; LBD = live birth delivery.

SUPPLEMENTAL TABLE IX Comparisons between subgroups of frozen embryo transfer cycles

Total frozen embryo transfer cycles				
Parameters	**Freeze-all**	**Surplus embryos**	**Total**	**P**
Patients (n)	122	195	317	
Cycles (n)	232	302	534	
CP (/FET) (rate)	49.6	42.7	45.7	.115
OP (/FET) (rate)	37.1	34.8	35.8	.582
LBD (/FET) (rate)	36.6	34.8	35.6	.655
Newborn (/FET) (rate)	40.5	38.1	39.1	.567
GnRHa frozen embryo transfer cycles				
Parameters	**Freeze-all**	**Surplus embryos**	**Total**	**P**
Patients (n)	110	129	239	
Cycles (n)	212	195	407	
CP (/FET) (rate)	49.5	44.1	46.9	.273
OP (/FET) (rate)	36.3	35.4	35.9	.844
LBD (/FET) (rate)	35.8	35.4	35.6	.922
Newborn (/FET) (rate)	38.7	38.5	38.6	.964
hCG frozen embryo transfer cycles				
Parameters	**Freeze-all**	**Surplus embryos**	**Total**	**P**
Patients (n)	12	66	78	
Cycles (n)	20	107	127	
CP (FET) (rate)	50.0	40.2	41.7	.414
OP (/FET) (rate)	45.0	33.6	35.4	.330
LBD (/FET) (rate)	45.0	33.6	35.4	.330
Newborn (/FET) (rate)	60.0	37.4	40.9	.059

Note: Significant differences between groups using human choriogonadotropin (hCG) or gonadotropin-releasing hormone agonist (GnRHa) as oocyte maturation trigger. Significance at P<.05.

FET = frozen embryo transfer cycles; CP = clinical pregnancy; OP = ongoing pregnancy; LBD = live birth delivery.

SUPPLEMENTAL TABLE X Comparisons between subgroups of frozen embryo transfer cycles (continued)

Freeze all embryo transfer cycles				
Parameters	**hCG**	**GnRHa**	**Total**	**P**
Patients (n)	12	110	122	
Cycles (n)	20	212	232	
CP (/FET) (rate)	50.0	49.5	49.6	.968
OP (/FET) (rate)	45.0	36.3	37.1	.442
LBD (/FET) (rate)	45.0	35.8	36.6	.417
Newborn (/FET) (rate)	60.0	38.7	40.5	.063
Frozen Surplus embryos transfer cycles				
Parameters	**hCG**	**GnRHa**	**Total**	**P**
Patients (n)	66	129	195	
Cycles (n)	107	195	302	
CP (/FET) (rate)	40.2	44.1	42.7	.511
OP (/FET) (rate)	33.6	35.4	34.8	.761
LBD (/FET) (rate)	33.6	35.4	34.8	.761
Newborn (/FET) (rate)	37.4	38.5	38.1	.854

Note: Significant differences between groups using human choriogonadotropin (hCG) or gonadotropin-releasing hormone agonist (GnRHa) as oocyte maturation trigger. Significance at P<.05.

FET = frozen embryo transfer cycles; CP = clinical pregnancy; OP = ongoing pregnancy; LBD = live birth delivery.

SUPPLEMENTAL TABLE XI Clinical outcomes per ART type, PCOS and PGT cycles

IVF *vs.* ICSI									
	hCG			**GnRHa**			**Total**		
ART type	**IVF**	**ICSI**	**P**	**IVF**	**ICSI**	**P**	**IVF**	**ICSI**	**P**
Patients (n)	78	143		134	297		212	440	
Cycles (n)	78	154		138	335		216	489	
ETC (n)	69	139		104	223		173	362	
CP (/ETC) (rate)	59.4	48.2	.127	58.7	61.9	.577	59.0	56.6	.610
OP (/ETC) (rate)	44.9	42.4	.734	44.2	51.6	.216	44.5	48.1	.441
LBD (/ETC) (rate)	43.5	42.4	.887	44.2	51.6	.216	43.9	48.1	.370
Newborn (/ETC) (rate)	56.5	52.5	.586	56.1	56.1	.178	51.4	54.7	.481
PCOS *vs.* non-PCOS									
	hCG			**GnRHa**			**Total**		
PCOS	**PCOS**	**no PCOS**	**P**	**PCOS**	**no PCOS**	**P**	**PCOS**	**no PCOS**	**P**
Patients (n)	29	192		131	300		160	492	
Cycles (n)	30	202		150	323		180	525	
ETC (n)	28	180		112	215		140	395	
CP (/ETC) (rate)	50.0	52.2	.827	60.7	60.9	.970	58.6	57.0	.741
OP (/ETC) (rate)	35.7	44.4	.386	50.9	47.9	.608	47.9	46.3	.756
LBD (/ETC) (rate)	32.1	44.4	.221	50.9	47.9	.608	47.1	46.3	.868
Newborn (/ETC) (rate)	50.0	54.4	.661	57.1	51.6	.343	55.7	52.9	.568
PGT vs non-PGT									
	hCG			**GnRHa**			**Total**		
PGT	**PGT**	**no PGT**	**P**	**PGT**	**no PGT**	**P**	**PGT**	**no PGT**	**P**
Patients (n)	16	205		25	404		41	609	
Cycles (n)	17	215		36	437		53	652	
ETC (n)	13	195		7	320		20	515	
CP (/ETC) (rate)	61.5	51.3	.474	57.1	60.9	1.000	60.0	57.3	.809
OP (/ETC) (rate)	61.5	42.1	.170	57.1	48.8	.718	60.0	46.2	.225
LBD (/ETC) (rate)	61.5	41.5	.158	57.1	48.8	.718	60.0	46.0	.219
Newborn (/ETC) (rate)	61.5	53.3	.566	71.4	53.1	.456	65.0	53.2	.299

Note: Significant differences between groups using human choriogonadotropin (hCG) or gonadotropin-releasing hormone agonist (GnRHa) as oocyte maturation trigger. Significance at P<.05.

ART = assisted reproductive technologies; IVF = *in vitro* fertilization; ICSI = intracytoplasmic sperm injection; ETC = embryo transfer cycles; CP = clinical pregnancy; OP = ongoing pregnancy; LBD = live birth delivery; PCOS = polycystic ovarian syndrome; PGT = preimplantation genetic testing.

SUPPLEMENTAL TABLE XII Clinical outcomes and karyotypes

Abnormal (abn) male karyotype (mK) *vs.* Normal (norm) male karyotype (mK)									
	hCG			**GnRHa**			**Total**		
Male Karyotype	**abn mK**	**norm mK**	**P**	**abn mK**	**norm mK**	**P**	**abn mK**	**norm mK**	**P**
Patients (n)	6	203		17	390		23	593	
Cycles (n)	7	212		18	431		25	643	
ETC (n)	7	188		12	298		19	486	
CP (/ETC) (rate)	57.1	52.7	1.000	60.0	62.1	1.000	52.6	58.4	.615
OP (/ETC) (rate)	42.9	44.1	1.000	33.3	49.7	.267	36.8	47.5	.360
LBD (/ETC) (rate)	42.9	43.6	1.000	33.3	49.7	.267	36.8	47.3	.369
Newborn (/ETC) (rate)	57.1	54.3	1.000	41.7	54.4	.387	47.4	54.3	.551
Abnormal (abn) female karyotype (fK) *vs.* Normal (norm) female karyotype (fK)									
	hCG			**GnRHa**			**Total**		
Female Karyotype	**abn fK**	**norm fK**	**P**	**abn fK**	**norm fK**	**P**	**abn fK**	**norm fK**	**P**
Patients (n)	6	206		12	399		18	605	
Cycles (n)	6	218		14	439		20	657	
ETC (n)	5	196		6	307		11	503	
CP (/ETC) (rate)	40.0	53.1	.669	50.0	60.6	.684	45.5	57.7	.541
OP (/ETC) (rate)	20.0	44.4	.388	33.3	48.5	.686	27.3	46.9	.196
LBD (/ETC) (rate)	20.0	43.9	.392	33.3	48.5	.686	27.3	46.7	.201
Newborn (/ETC) (rate)	20.0	55.1	.181	50.0	53.1	1.000	36.4	53.9	.249
Klinefelter (KS) *vs.* Normal (norm) male karyotype (mK)									
	hCG			**GnRHa**			**Total**		
Klinefelter syndrome	**KS**	**norm mK**	**P**	**KS**	**norm mK**	**P**	**KS**	**norm mK**	**P**
Patients (n)	2	203		2	390		2	593	
Cycles (n)	2	212		10	431		12	643	
ETC (n)	2	188		8	298		10	486	
CP (/ETC) (rate)	50.0	52.7	1.000	62.5	62.1	1.000	60.0	58.4	1.000
OP (/ETC) (rate)	50.0	44.1	1.000	37.5	49.7	.723	40.0	47.5	.755
LBD (/ETC) (rate)	50.0	43.6	1.000	37.5	49.7	.723	40.0	47.3	.755
Newborn (/ETC) (rate)	50.0	54.3	.502	50.0	54.4	1.000	60.0	54.3	.761

Note: Significant differences between groups using human choriogonadotropin (hCG) or gonadotropin-releasing hormone agonist (GnRHa) as oocyte maturation trigger. Significance at P<.05.

ETC = embryo transfer cycles; CP = clinical pregnancy; OP = ongoing pregnancy; LBD = live birth delivery.

SUPPLEMENTAL TABLE XIII Clinical outcomes related to sperm origin

Fresh ejaculated sperm (Ejac) *vs.* total Fresh testicular sperm (Test)									
	hCG			**GnRHa**			**Total**		
	Ejac	**Test**	**P**	**Ejac**	**Test**	**P**	**Ejac**	**Testis**	**P**
Patients (n)	189	22		335	68		524	90	
Cycles (n)	197	26		368	74		565	100	
ETC (n)	173	26		255	52		428	78	
CP (/ETC) (rate)	52.0	42.3	.356	62.4	55.8	.374	58.2	51.3	.258
OP (/ETC) (rate)	44.5	30.8	.187	51.8	44.2	.322	48.8	39.7	.139
LBD (/ETC) (rate)	43.9	30.8	.205	51.8	44.2	.375	48.6	39.7	.172
Newborn (/ETC) (rate)	55.5	38.5	.105	55.7	48.1	.315	55.6	44.9	.080
Fresh ejaculated sperm (Ejac) *vs.* Fresh testicular sperm (TESE)									
	hCG			**GnRHa**			**Total**		
	Ejac	**TESE**	**P**	**Ejac**	**TESE**	**P**	**Ejac**	**TESE**	**P**
Patients (n)	189	12		335	30		524	42	
Cycles (n)	197	15		368	31		565	46	
ETC (n)	173	15		255	22		428	37	
CP (/ETC) (rate)	52.0	53.3	.922	62.4	68.2	.587	58.2	62.2	.637
OP (/ETC) (rate)	44.5	33.3	.402	51.8	54.5	.802	48.8	45.9	.736
LBD (/ETC) (rate)	43.9	33.3	.427	51.8	54.5	.802	48.6	45.9	.799
Newborn (/ETC) (rate)	55.5	33.3	.510	55.7	63.6	.471	55.6	56.8	.893
Fresh ejaculated sperm (Ejac) *vs.* Frozen testicular sperm (TESEc)									
	hCG			**GnRHa**			**Total**		
	Ejac	**TESEc**	**P**	**Ejac**	**TESEc**	**P**	**Ejac**	**TESEc**	**P**
Patients (n)	189	1		335	9		524	10	
Cycles (n)	197	1		368	10		565	11	
ETC (n)	173	1		255	5		428	6	
CP (/ETC) (rate)	52.0	0		62.4	60.0	1.000	58.2	50.0	.699
OP (/ETC) (rate)	44.5	0		51.8	60.0	1.000	48.8	50.0	1.000
LBD (/ETC) (rate)	43.9	0		51.8	60.0	1.000	48.6	50.0	1.000
Newborn (/ETC) (rate)	55.5	0		55.7	60.0	1.000	55.6	50.0	1.000

Note: Significant differences between groups using human choriogonadotropin (hCG) or gonadotropin-releasing hormone agonist (GnRHa) as oocyte maturation trigger. Significance at P<.05.

ETC = embryo transfer cycles; CP = clinical pregnancy; OP = ongoing pregnancy; LBD = live birth delivery.

SUPPLEMENTAL TABLE XIV Clinical outcomes related to sperm origin (continued)

Fresh ejaculated sperm (Ejac) *vs.* Fresh testicular sperm (TESA)									
	hCG			**GnRHa**			**Total**		
	Ejac	**TESA**	**P**	**Ejac**	**TESA**	**P**	**Ejac**	**TESA**	**P**
Patients (n)	189	9		335	29		524	38	
Cycles (n)	197	10		368	33		565	43	
ETC (n)	173	10		255	25		428	35	
CP (ETC) (rate)	52.0	30	.207	62.4	44	.073	58.2	40	**.037**
OP (/ETC) (rate)	44.5	30	.517	51.8	32	.059	48.8	31.4	**.047**
LBD (/ETC) (rate)	43.9	30	.518	51.8	32	.059	48.6	31.4	.050
Newborn (/ETC) (rate)	55.5	30	.190	55.7	32	**.023**	55.6	31.4	**.006**
Fresh ejaculated sperm (Ejac) *vs.* Frozen ejaculated homologous sperm (FH)									
	hCG			**GnRHa**			**Total**		
	Ejac	**FH**	**P**	**Ejac**	**FH**	**P**	**Ejac**	**FH**	**P**
Patients (n)	189	3		335	5		524	8	
Cycles (n)	197	3		368	1		565	8	
ETC (n)	173	3		255	1		428	4	
CP (/ETC) (rate)	52.0	66.7	1.000	62.4	100	1.000	58.2	75.0	.644
OP (/ETC) (rate)	44.5	66.7	.588	51.8	0		48.8	50.0	1.000
LBD (/ETC) (rate)	43.9	66.7	.585	51.8	0		48.6	50.0	1.000
Newborn (/ETC) (rate)	55.5	100	.258	55.7	0		55.6	50.0	.633
Fresh ejaculated sperm (Ejac) *vs.* Donor sperm (D)									
	hCG			**GnRHa**			**Total**		
	Ejac	**D**	**P**	**Ejac**	**D**	**P**	**Ejac**	**D**	**P**
Patients (n)	189	7		335	23		524	30	
Cycles (n)	197	7		368	23		565	30	
ETC (n)	173	6		255	16		428	22	
CP (/ETC) (rate)	52.0	83.3	.216	62.4	50.0	.324	58.2	59.1	.932
OP (/ETC) (rate)	44.5	50.0	1.000	51.8	25.0	**.038**	48.8	31.8	.119
LBD (/ETC) (rate)	43.9	50.0	1.000	51.8	25.0	**.044**	48.6	31.8	.180
Newborn (/ETC) (rate)	55.5	50.0	1.000	55.7	31.3	.057	55.6	36.4	.077

Note: Significant differences between groups using human choriogonadotropin (hCG) or gonadotropin-releasing hormone agonist (GnRHa) as oocyte maturation trigger. Significance at P<.05.

ETC = embryo transfer cycles; CP = clinical pregnancy; OP = ongoing pregnancy; LBD = live birth delivery.

SUPPLEMENTAL TABLE XV Associations of selected outcomes with trigger (GnRHa vs. hCG) from univariable and multivariable logistic regression

	Odds Ratio	95%CI	P	Adjusted Odds Ratio*	95%CI	P
ETC[a]						
CP (/ETC)	1.440	1.013 to 2.045	**0.042**	1.186	0.775 to 1.814	0.432
OP (/ETC)	1.256	0.886 to 1.782	0.201	1.118	0.730 to 1.712	0.607
LBD (/ETC)	1.281	0.903 to 1.818	0.165	1.139	0.744 to 1.745	0.550
Have a new born (/ETC)	1.241	0.875to 1.760	0.226	1.095	0.715 to 1.677	0.676
FET[b]						
CP (/FET)	1.235	0.825 to 1.847	0.305	1.522	0.953 to 2.431	0.079
OP (/FET)	1.019	0.672 to 1.546	0.928	1.238	0.759 to 2.018	0.393
LBD (/FET)	0.998	0.658 to 1.513	0.991	1.205	0.739 to 1.965	0.455
Have a newborn (/FET)	1.019	0.672 to 1.546	0.928	1.238	0.759 to 2.018	0.393
ETC+FET[c]						
CP (/cycle)	1.424	1.025 to 1.977	**0.035**	1.357	0.921 to 2.000	0.123
OP (/cycle)	1.225	0.892 to 1.681	0.209	1.134	0.777 to 1.654	0.516
LBD (/cycle)	1.214	0.885 to 1.666	0.230	1.117	0.765 to 1.631	0.565
Have a newborn (/cycle)	1.214	0.885 to 1.666	0.230	1.119	0.766 to 1.632	0.561

Note: Significant differences between groups using human choriogonadotropin (hCG) or gonadotropin-releasing hormone agonist (GnRHa) as oocyte maturation trigger. Significance at P<.05. OR>1 represents it is more likely to achieve the outcome (CP, OP, LBD or have a newborn) with GnRHa than with hCG.

* After adjusting for age, AMH, and number of follicles, [a] N=535 (univariable regression), N=458 (multivariable regression), [b] N=534 (univariable regression), N=492 (multivariable regression), [c] At least one outcome per initiated cycle and associated FET, N=706 (univariable regression), N=619 (multivariable regression).

ETC = embryo transfer cycles; FET = frozen-thawed embryo transfer cycles; iFET = intended frozen-thawed embryo transfer cycles; CP = clinical pregnancy; OP = ongoing pregnancy; LBD = live birth delivery

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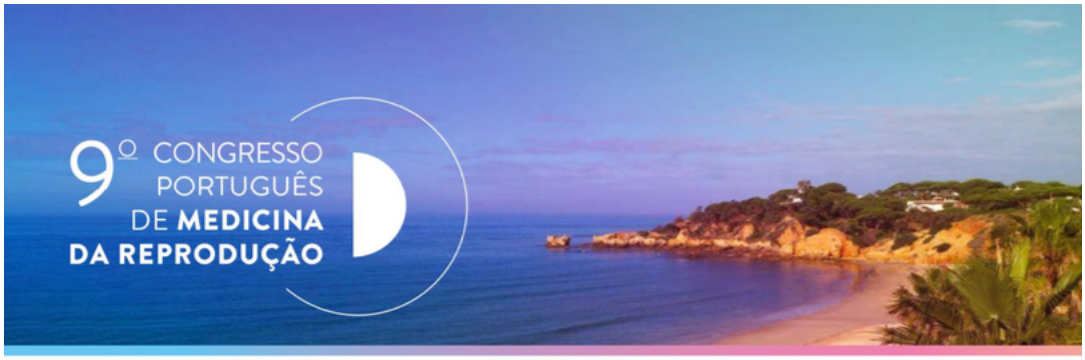
Annex I – Poster presentation: 9º Congresso Português de Medicina da Reprodução



CERTIFICADO

Para os devidos efeitos certifica-se que o trabalho

IMPACTO DO TRIGGER DA MATURAÇÃO OVOCITÁRIA NOS RESULTADOS DOS TRATAMENTOS DE INFERTILIDADE EM ALTAS-RESPONDEDORAS

elaborado por

Maria da Silva Gonçalves; Mariana Cunha; José Teixeira da Silva; Joaquina Silva; Paulo Viana; Cristiano Oliveira; Alberto Barros; Mário Sousa

foi apresentado como **Poster** no ***9º Congresso Português de Medicina da Reprodução***, que decorreu de 09 a 11 de maio de 2024, no Hotel Grande Real Santa Eulália.

Albufeira, 11 de maio de 2024

Prof. Doutor Pedro Xavier
Presidente do Congresso

Organização

SPMR SOCIEDADE PORTUGUESA DE MEDICINA DA REPRODUÇÃO

Annex 2 – Poster presentation: 17th Encontro de Investigação Jovem da U.Porto (IJUP)

ENCONTRO
INVESTIGAÇÃO JOVEM

8, 9 e 10 MAIO 2024

FACULDADE DE ECONOMIA
UNIVERSIDADE DO PORTO

CERTIFICADO

Certifica-se que **Maria Gonçalves** participou no **IJUP'24 – 17º Encontro de Investigação Jovem da Universidade do Porto**, que decorreu nos dias 08, 09 e 10 de maio de 2024, tendo apresentado um póster com o título ***"hCG and GnRH agonist – oocyte maturation trigger's impact on infertility treatment outcomes in high-responders: a report on 705 cycles"***.

Vice-Reitor

Organização

Apoio

Final Considerations and Future Perspectives

The importance of this work lies in its exploration of a subset of patients that, although at particular risk for complications, is underexplored in current literature. For that purpose, we presented more complete data than most studies, analyzing not only fresh embryo transfer cycles, but also frozen-thawed embryo transfers, and presenting cumulative rates.

Our investigation must also function as a call to define the high-responder population, properly manage the treatment cycles of these patients, and, therefore, provide the best clinical outcomes while minimizing risks.

GnRH-agonists, as oocyte maturation triggers, associated with adequate luteal phase support, have been consecutively found to perform similarly to hCG, in some cases with surprisingly improved outcomes reported. Therefore, it is our recommendation to broaden this strategy's use in clinical practice.

We consider that the best controlled ovarian stimulation protocols and oocyte maturation triggers must continue to be investigated and innovated in order to perform embryo transfer cycles without the need for cryopreservation. Nevertheless, we suggest that freeze-all must be more frequently considered as an approach to cycles in identified high-responder patients, to reduce OHSS incidence.

In future investigations, even larger and more representative populations, preferably from different fertility centers, should be analyzed prospectively to sustain the conclusions from this report.

Biographical and Curricular Résumé

Maria Gonçalves is a sixth year Medical Student, at ICBAS - Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Unidade Local de Saúde de Santo António and a Clinical Researcher at the Unit BGR/MCM - Biology and Genetics of Reproduction/Molecular and Cellular Medicine at the UMIB - Unidade Multidisciplinar de Investigação Biomédica/ITR - Laboratory for Integrative and Translational Research in Population Health, Universidade do Porto.

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