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Administração de hormônio do crescimento para melhorar os resultados reprodutivos em mulheres com falha de implantação recorrente (RIF): a revisão sistemática

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MAIRA ALEJANDRA VERA MONTOYA

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Administração de hormônio do crescimento para melhorar os resultados reprodutivos em mulheres com falha de implantação recorrente (RIF): a revisão sistemática

Dissertação apresentada ao Programa de Pós-Graduação em Saúde da Mulher da Universidade Federal de Minas Gerais como requisito para obtenção do título de Mestre.

Orientador: Prof. Dr. Selmo Geber
Co-orientadora: Prof. Dr. José Andrés Calvache

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Realizou-se, no dia 26 de novembro de 2021, às 10:00 horas, Online, da Universidade Federal de Minas Gerais, a defesa de dissertação, intitulada *Administração de hormônio do crescimento para melhorar os resultados reprodutivos em mulheres com falha de implantação recorrente (RIF) revisão sistemática*, apresentada por MAIRA ALEJANDRA VERA MONTOYA, número de registro 2020661750, graduada no curso de MEDICINA, como requisito parcial para a obtenção do grau de Mestre em SAÚDE DA MULHER, à seguinte Comissão Examinadora: Prof(a). Fernando Marcos dos Reis - Orientador (UFMG), Prof(a). Melissa Orlandin Premaor (UFMG), Prof(a). Túlio Pinho Navarro (UFMG).

A Comissão considerou a dissertação:

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Prof(a). Melissa Orlandin Premaor (Doutora)

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RESUMO

A falha de implantação recorrente (RIF) tem sido usada para descrever a falha de implante de embriões após a fertilização in vitro, levantando preocupações quanto à importância de seu tratamento. O hormônio do crescimento (GH) tem sido estudado como uma das possíveis co-intervenções. Nossa revisão atualizada avaliou a intervenção com GH vs. nenhuma intervenção de ensaios clínicos randomizados (RCTs) em pacientes com RIF. Pesquisas eletrônicas sobre The Menstrual Disorders and Subfertility Group (MDSG), The Cochrane Central Register for Clinical Trials, PubMed MEDLINE, Ovid EMBASE, PsycINFO, CINAHL, LILACS, e o Google Scholar até junho de 2020 identificou 2 RCTs, compilados com os critérios de inclusão acima. O risco de viés (RoB) e a qualidade das evidências foram avaliados de acordo com a ferramenta de colaboração Cochrane e as diretrizes do grupo GRADE. A metanálise encontrou taxas mais altas de gravidez clínica (OR: 4,97 IC 95% 2,05 a 12,05 I^2: 0%), nascidos vivos (OR: 5,13 IC 95% 2,03 a 12,91 I^2: 0%) quando comparado com GH para Sem intervenção. No entanto, esta revisão não pode fornecer uma recomendação forte devido à qualidade da evidência classificada como "qualidade de evidência muito baixa" em todos os resultados selecionados portanto, recomenda-se aos médicos individualizar o caso de cada paciente para considerar a relevância do tratamento apresentado. Enfatizamos a importância das próximas pesquisas em pacientes com RIF, que pode ser uma minoria, ainda é um dos maiores impactos na qualidade de vida.

Palavras-chave: Hormônio de crescimento, Falha recorrente de implantação, Revisão sistemática, Metanálise

ABSTRACT

Recurrent implantation failure (RIF) has been used to describe embryos' failure to implant following IVF, arising concerns to the importance of its treatment. Growth hormone (GH) has been studied as one of the possible co-interventions. Our updated review evaluated GH intervention vs. No intervention from randomized controlled trials (RCTs) in RIF patients. Electronic searches on The Menstrual Disorders and Subfertility Group (MDSG), The Cochrane Central Register for Clinical Trials, PubMed MEDLINE, Ovid EMBASE, PsycINFO, CINAHL, LILACS. and Google Scholar up to June 2020 identified 2 RCTs, compiled with the above inclusion criteria. The Risk of Bias (RoB) and the quality of evidence was assessed according to the Cochrane Collaboration tool and GRADE group guidelines. Metanalysis found higher rates of clinical pregnancy (OR: 4.97 CI 95% 2.05 to 12.05 I^2: 0%), live birth (OR: 5.13 CI 95% 2.03 to 12.91 I^2: 0%), when compared GH to No intervention. However, this review cannot provide a strong recommendation due to the quality of evidence rated as "very low quality of evidence" in all the outcomes we selected, therefore we recommend all physicians to individualize each patient in their need or possible benefit with this co-intervention. We emphasize the importance of upcoming research in RIF patients, which may be a minority; it is still one of the highest impacts on life quality.

Key-words: Growth hormone, Recurrent implantation failure, Systematic review, Metanalysis.

LISTA DE ABREVIATURAS E SIGLAS

ART:	assisted reproduction technologies
ASRM:	American Society for Reproductive Medicine
BMI:	body mass index
CI:	confidence interval
CPR:	clinical pregnancy rate
ESHRE:	European Society of Human Reproduction and Embryology
ET:	embryo transfer
FSH:	follicle stimulating hormone
GH:	growth hormone
GhRH:	gonadotropin-releasing hormone
GRADE:	Grading of Recommendations, Assessment, Development and Evaluation
hCG:	human chorionic gonadotropin
HRT:	hormone replacement therapy
ICSI:	intracitoplasmatic sperm injection
IGF-1:	insulin growth factor 1
IM:	intramuscular
IR:	implantation rate
ITGB3:	integrin beta 3
IU:	international units
IVF:	in vitro fertilization
LBR:	live birth rate

LH: luteinizing hormone

MDSG: The Menstrual Disorders and Subfertility Group

MPR: multiple pregnancy rate

MR: miscarriage rate

OR: odds ratio

PGD: preimplantation genetic diagnosis

POR: poor ovarian responders

RCTs: randomized controlled trials

RIF: recurrent implantation failure

RoB: risk of bias tool

SC: subcutaneous

StAR: steroidogenic acute regulatory protein

VEGF: vascular endothelial growth factor

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SUMÁRIO

1. Introduction

In assisted reproduction technologies (ART), such as in vitro fertilization (IVF), embryo implantation is a crucial step to achieve pregnancy and posterior live birth. Implantation is a complex human reproduction processes and it is affected by endometrium, embryo, and mostly the synchrony between them (1,2,3,4). When that synchrony is absent, it can lead to implantation failure without any apparent etiology (5,6). The term recurrent implantation failure (RIF) has been used to describe the failure of embryos to implant following IVF; nevertheless, there is no consensus about its definition, leading to misdiagnosis and also potential over-diagnosis (7,8,9,10,11). One of the most accepted definitions provided by The ESHRE PGD consortium mention that RIF could be considered as the failure in achieving pregnancy after more than three high-quality embryo transfers (ETs) or implantation failure with the transfer of ≥10 embryos multiple transfers; with exact numbers to be determined by each center (12). In addition, RIF treatment is also a reason for several discussions. There is not a single intervention defined as the standard treatment or any based on high-quality evidence. Still, the research in RIF is growing, since many authors are concerned about reproductive outcomes in these patients. (13,14,15,16).

As mentioned, endometrial receptivity is a pivotal action in implantation. Estrogen and progesterone's synergistic actions orchestrate this receptivity, as well as, endocrine, paracrine, and autocrine factors (17,18,19,20,21). Some of these autocrine and endocrine factors are Growth Hormone (GH) and local Insulin Growth Factor 1 (IGF-1), a known downstream mediator of growth hormone (22,23). Studies about GH's effect in the endometrium have shown that it might

act in a direct or IGF-1-mediated manner on endometrial cells to promote proliferation, vascularization (23,24,25,26); also, on up-regulation receptivity-related genes such as vascular endothelial growth factor (VEGF), an essential player in angiogenesis (27,28,29); and integrin beta 3 (ITGB3), a well-known biomarker of receptivity, whose down-regulation is related to lower pregnancy rates (30,31,32,33). Besides its effect on endometrial receptivity, there is also evidence about GH's indirect effect on ovarian function, mainly its involvement in the function and maintenance of the corpus luteum and progesterone production (34,35,36).

These many roles open the door for GH's clinical use in patients undergoing ART. Therefore, its use has been studied in several patients, especially patients with poor prognosis or complications in previous cycles, including poor ovarian responders (POR) (37,38,39,40), patients with thin endometrium (41,42,43), and patients with poor ovarian reserve and low oocyte quality (44,45). Showing suitable effects in these patients and favoring GH supplementation as a co-therapy to improve clinical and reproductive outcomes, mostly by its impact in endometrial receptivity. Since endometrial asynchrony is proposed as an etiology for RIF, GH supplementation also seems like a potential treatment for these patients (5,23).

RIF represents a challenging and frustrating condition. Physicians have to handle stressed couples who are frequently overwhelmed by the situation where implantation failure has a significant impact on their physical, mental health, and their family as in their quality of life (46). Failure to achieve pregnancy is one of the main reasons explaining the high rate (up to 50%) of couples who drop-out

from ART programs after fewer than three cycles (47,48), making them extremely vulnerable and susceptible to may consent to undergo expensive and unsupported procedures that can expose them to undue risks (49).

Thus, this systematic review and meta-analysis aims to evaluate GH administration's efficacy and safety as a co-treatment in women with RIF undergoing ART, using the PICO question structure to formulate our review question, being P(population) women with RIF; I(intervention) GH administration; C(comparison) no intervention or placebo; and O(outcome) clinical pregnancy rate as our primary outcome.

2. Materials and Methods

2.1. PROSPERO registration

Our systematic review was registered with PROSPERO of the National Institute for Health Research (www.crd.york.ac.uk), registration number CRD42020195818.

2.2. Literature search

Online searches of databases were performed in The Menstrual Disorders and Subfertility Group (MDSG), The Cochrane Central Register for Clinical Trials, PubMed MEDLINE, Ovid EMBASE, PsycINFO, CINAHL, LILACS. and Google Scholar (for gray literature) up to June 2020. The searches also included databases for registered and ongoing trials. A combination of Medical Subject Headings and words were used to generate a subset of: citations for growth hormone ("growth hormone administration", "growth hormone"); citations including RIF ("recurrent implantation failure", "repeated implantation failure", "implantation failure", "implantat*) (Table 1). These subsets were combined using 'AND' to generate final citations addressing the research question. We scanned the reference lists and citations of included trials and any relevant systematic reviews identified for further additional trials. No time or language restrictions were placed on the searches, for all non-English articles of the relevant studies. Authors were contacted to obtain further information, as appropriate.

Table 1. Full search strategies of databases

Pubmed: 179 (((((((((("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type]) OR "randomized"[Title/Abstract]) OR "placebo"[Title/Abstract]) OR "drug therapy"[MeSH Subheading]) OR "randomly"[Title/Abstract]) OR "trial"[Title/Abstract]) OR "groups"[Title/Abstract]) NOT ("animals"[MeSH Terms] AND (((((((Adult women) AND (RIF)) OR (Recurrent implantation failure)) OR (Repeated implantation failure)) OR (Implantation failure)) OR (Implantat*)) AND ((("growth hormone"[MeSH Terms]) OR ("growth hormone administration"[All Fields])) OR (growth hormone)))
EMBASE: 33 ('recurrent implantation failure' OR 'repeated implantation failure') AND growth AND hormone
CINHALS: 22 TX embryo transfer AND TX implantation AND TX growth hormone Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text
ClinicaTrials 0 studies found for recurrent implantation failure and growth hormone 54 studies found for RIF but none about growth hormone treatment
ICTRP (WHO portal) 82 studies found for recurrent implantation failure But none about growth hormone

2.3. Study eligibility criteria

We included randomized controlled trials (RCTs) that compared the use of GH (intervention) with placebo or no adjuvant treatment in women with RIF undergoing ART. Due to the lack of consensus in RIF's definition, we accepted the definition used by each study's authors. We excluded non-randomized studies, observational studies, retrospective studies, and GH use in non-RIF study populations. Two authors (M.V.M. and J.A.C.) independently performed the study selection and data extraction; all articles, including abstracts from the electronic searches, were assessed, and citations that met the initial pre-defined selection criteria were obtained. Final inclusion-exclusion decisions were made after examination of full manuscripts. After an independent review of the documents,

any disagreement between the two reviewers was resolved by consultation with a third reviewer (S.G.).

2.4. Study quality assessment

The selected studies were assessed for the methodological quality using the domain-based risk of bias assessment tool recommended by the Cochrane Collaboration (50). Information was sought on the method of randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. For each study, information was obtained on the participants with RIF diagnosis, intervention used (GH), and intervention timing related to the treatment cycle. Where there was doubt or lack of information, authors were contacted for further details.

2.5. Outcome measurements

The primary outcome measure was clinical pregnancy rate per woman (CPR). Secondary outcome measures were live birth rate (LBR), miscarriage rate (MR), congenital abnormalities, and multiple pregnancy rate (MPR). Other reported observations were drug (GH) related side effects, implantation rate (IR), number of embryos obtained and, endometrial thickness. Live birth rate was calculated as the number of births by the number of patients included in each group. IR was defined as the number of gestational sacs divided by the number of embryos transferred. CPR was defined as gestational sac and fetal heart activity seen per woman on a transvaginal ultrasound scan. MPR was defined as the

number of multiple pregnancies divided by the total number of clinical pregnancies. Miscarriage rate was defined as the loss of pregnancy after the identification of clinical pregnancy per woman.

2.6. Data extraction, statistical analysis and summary of findings

Study features and outcomes were assembled in a tabular form, and formal meta-analysis was performed using Review Manager (RevMan®, version 5.4). A random-effects model was used, as clinical and methodological heterogeneity across studies were expected. The I2 statistic was used to assess heterogeneity. The effect estimate was expressed as an odds ratio (OR) with a 95% confidence interval (CI) and was represented graphically by forest plots. We were not able to assess publication bias visually due to the small number of included studies.

We presented our results using the GRADE approach (51,52,53). We downgraded the quality of evidence from high-quality to moderate-, low- or very low-quality. Downgrading was undertaken independently by two review authors (MVM and JAC) and agreement reached by consensus. Characteristics of the evidence that caused downgrading include: 1. limitations in the design and implementation of available studies, suggesting a high likelihood of bias (for example, studies not using a double dummy placebo design); 2. indirectness of evidence (indirect population, intervention, control or outcomes); 3. inconsistency of results; 4. imprecision of results (wide confidence intervals). When one of the above items was assessed as a risk, the evidence was downgraded by two levels (very serious risk) or one level (serious risk). We used the following interpretations

of this assessment of quality of evidence for our primary outcome: 1) High quality: Further research is very unlikely to alter the confidence in the estimate of the effect; 2) Moderate quality: Further research is likely to alter the confidence in the estimate of the effect; 3) Low quality: Further research is very likely to alter the confidence in the estimate of the effect; 4) Very low quality: The confidence in the effect estimate is very little.

3. Results

3.1. Search results

Literature searches and selection of studies for the analysis is shown in Fig. 1. Studies were selected and reported according to the PRISMA guidelines (54). Of 183 citations identified, 23 were selected for detailed evaluation, and finally, two RCTs were included in the analysis. Although two studies met the inclusion criteria, there were differences in defining RIF. Altmäe et al. (55) described RIF with two failed oocyte donation attempts. In contrast, Chen et al. (56) defined RIF as the failure of pregnancy despite the implantation of a high-quality embryo at least three times or over ten embryos on repeat implantation. Similarly, there was a difference in the study population, those in an oocyte donation program (Altmäe et al. 2018) and those with proper oocyte transfers (Chen et al. 2018).

3.2. Study quality assessment and publication bias

Included studies were published at 2010 onwards. The two RCTs (Altmäe et al., 2018; Chen et al., 2018) were at "unclear risk" for random sequence generation and allocation concealment since they did not mention any clear statement about their random sequence generation neither the allocation concealment. Both studies were at "low risk of bias" for blinding of participants and personnel, blinding of outcomes assessment and incomplete outcome data; because the assessment for pregnancy-related outcomes is unlikely to be subjective or affected by blinding, since implantation, clinical pregnancy, live birth, and miscarriage are all objectively assessed. The risk was also "low risk" for

attrition bias (Fig. 2), given the fact that neither studies presented missing outcome data. In the study by Altmäe et al. 2018, the risk for publication (reporting) bias was low since we could compare the reported outcomes to the published protocol; as we could not do with the Chen et al. study, despite contacting the authors, so we classified it as "unclear risk."

Figure 1. PRISMA Flow diagram

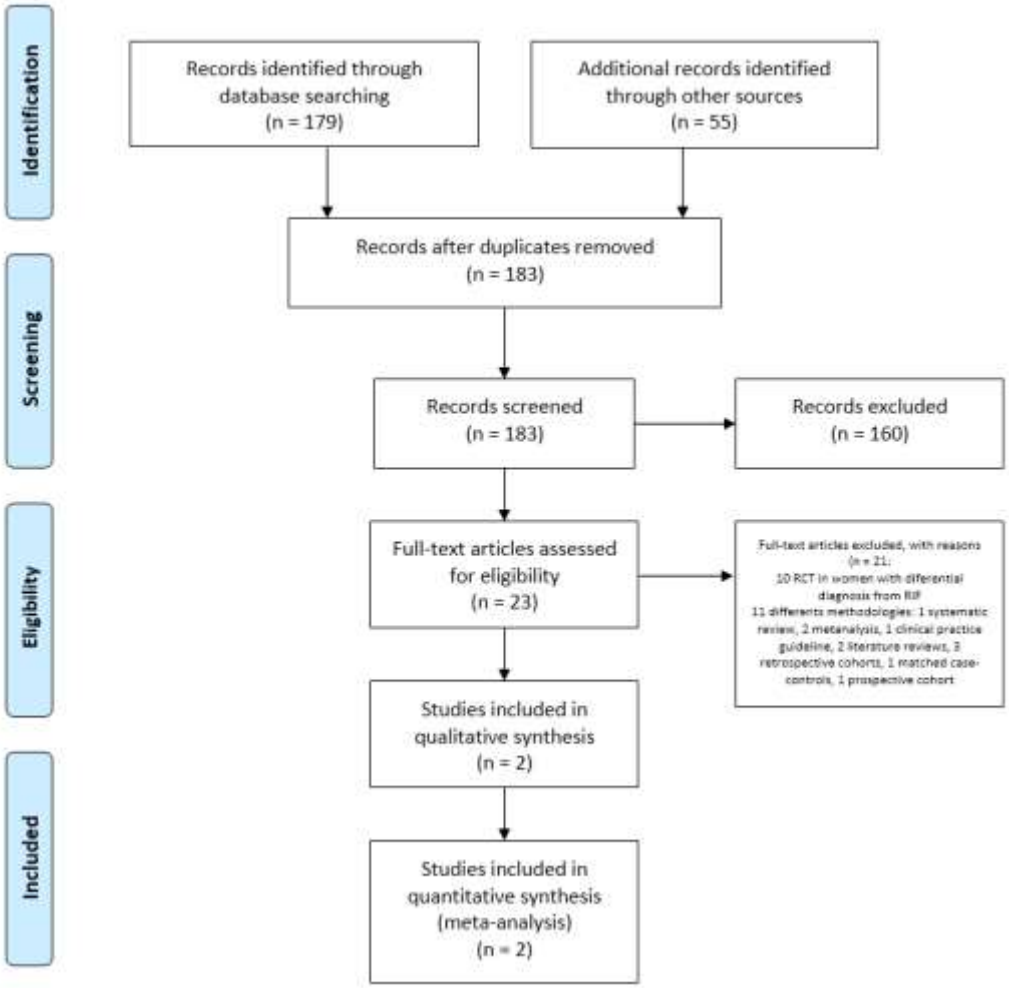
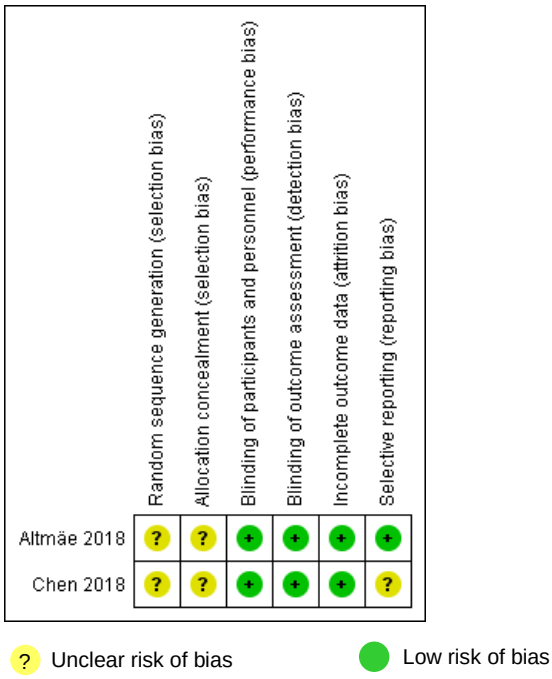


Figure 2. Risk of Bias Assessment:



3.3. Included and excluded studies

The main characteristics of included and excluded studies are in tables 2 and 3 respectively. Both studies included a population of women with RIF diagnosis, although the definition of RIF was different; Altmäe et al. developed their study in an oocyte-donation program setting and had a mean age of around 42 years, while Chen et al. had a mean age of 34 years old. All patients received hormone-replacement protocol for ovarian stimulation. Both studies used human chorionic gonadotropin (hCG) to trigger ovulation. The oocytes were retrieved 34-36 hours later, in both studies, either donated or proper oocytes, and had fresh embryo transfers. GH was administrated in the treatment groups of both studies and was compared with no intervention group. The primary outcomes were pregnancy rate, live birth rate, and live-born baby rate for Altmäe et al. and clinical pregnancy and live birth rate for Chen et al.

Altmäe et al. performed a randomized controlled trial in women with RIF, defined by two failed oocyte-donation attempts, from 2010 to 2017; the authors excluded donors older than 25 years and recipients older than 52. They included 105 couples, 70 couples with RIF, and 35 at their first cycle (we excluded from these patients from the analysis since they did not have diagnosis of RIF). The study population consisted of 35 women who received GH 3 IU/day for ten consecutive days, adjusting to give the last injection one or two days before starting vaginal progesterone (57). The oocyte donors were stimulated using a long gonadotropin-releasing hormone (GnRH) agonist protocol and human recombinant follicle-stimulating hormone. Human menopausal gonadotropin was added when plasma luteinizing hormone (LH) concentration was <1 IU/L. Final oocyte maturation was triggered by 250 µg hCG SC, when five follicles measured 18 mm or more. Ovarian puncture for oocyte recovery was performed 36.5 hours after recombinant hCG injection. Oocyte recipients were treated with progressively increasing doses of oral pure estradiol or estradiol valerate after previous pituitary desensitization with a single injection of the long-acting preparation GnRH agonist (triptorelin 3.75 mg); the interval between triptorelin injection and the beginning of oral estradiol treatment ranged between 8 and 20 days, individually decided for each patient to optimize the synchronization between donor and recipient.

Chen et al. included in their study 42 patients with RIF, defined as a failure of pregnancy despite implantation of a high-quality embryo at least 3 times, or of

over 10 embryos on repeat implantation, from April to October of 2012; the exclusion criteria included prior endometrial resection or endometrial polyps, positive for an autoimmune antibody (anticardiolipin antibody), presence of infectious disease, hyperthyroidism and (or) hyperprolactinemia, chromosomal abnormalities or thalassemia evident in both sexual partners, and other malefactors. All patients received 1.25mg GnRH. The treatment group received GH (4 U/day) until the day of hCG administration. Follicle growth was monitored via vaginal scan ultrasound. When the follicle diameter exceeded 18 mm, 6000–10000 IU hCG were administered by IM injection. Oocytes were retrieved 34–36 h later, and embryo implantation performed three days later.

Table 2. Main characteristics of included studies in the review

Study	Participants	Intervention	Control	Outcomes
Altmäe et al. 2018	2 failed oocyte donation attempts (defined as RIF). Upper limit of oocyte recipient age and of oocyte donor age: 52 years and 25 years respectively. Mean age in GH group: 42.2 (SD: 4.7), non-GH group: 42.4 (SD: 3.7). 35 cases and 35 controls, 35 positive controls were patients in their first oocyte donation cycle (were excluded from this review). Only fresh embryos were transferred.	GH (3 IU/day) 10 consecutive days. The last injection was administered 1 or 2 days before starting progesterone.	No treatment	CPR, LBR, IR, MR, endometrial thickness, number of embryos obtained, live born baby rate
Chen et al. 2018	3 implantation attempts of a high-quality embryo, or of over 10 embryos on repeat implantation (defined as RIF). Normal hormone levels, and no use of synthetic hormones in the 3 months prior to study entry. Mean age in GH group: 33.89 (SD: 2.93) Control group 34.03 (SD: 3.42). 22 cases and 20 controls.	GH (4 IU/day) until the day of hCG administration	No treatment	CPR, LBR, IR, MR, endometrial thickness, relative expression level of GHR mRNA in granulosa cells, GH level of follicular fluid, expression levels of StAR mRNA in granulosa cells

RIF: recurrent implantation failure; GH: growth hormone; CPR: clinical pregnancy rate; LBR: live birth rate; IR: implantation rate; MR: miscarriage rate.

Table 3. Main characteristics of excluded studies in the review

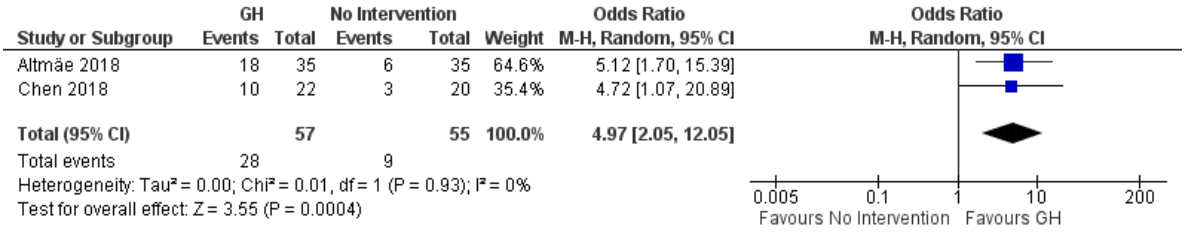
Study	Design	Participants	Intervention	Control	Exclusion criteria
Wang et al. 2016	Non-randomized	230 women undergoing their first cycle of frozen-thawed embryo transfer	Patients were divided in 3 groups: - A not received GH - B: 4 IU GH/day SC simultaneously with HRT until progesterone injection - C: 4 IU GH/day SC from day 8 of HRT until progesterone injection	No treatment Different dosage	Not RIF
Younis et al. 1992	RCT	42 normal ovulatory, women ≤38 years, with mechanical factor infertility and a normal male factor	12 IU GH/day SC on days 1, 3, 5, and 7 of hCG treatment	Placebo	Not RIF
Ho et al. 2017	Retrospective cohort	436 women in total: 134 women of advanced age. 236 women with one or more IVF previous treatment failures, 66 women with POR	3 IU/GH/day SC from cycle day 3 when gonadotrophin was started to the day of hCG	No treatment	Retrospectiv e design
Choe et al. 2018	RCT	127 women who met Bologna criteria for POR	4 IU GH (20mg)/day SC on mid-luteal, late luteal, and menstrual cycle day 2	No treatment	Not RIF
Tesarik et al. 2005	RCT	100 women >40 years entering an assisted reproduction program. Extreme azoospermia was excluded	8 IU/GH/day SC from day 7 of gonadotrophin administration until the day following hCG	Placebo	Not RIF
Li et al. 2020	RCT	158 women with poor embryo development	3 IU/GH/day SC from the initial day of downregulation for the long protocol or stimulation for the antagonist protocol until the day of the hCG	No treatment	Not RIF
Eftekar et al. 2013	RCT	82 women with POR selected for ART	4 IU GH/day SC from day 21 of previous cycle until the day of the hCG	No treatment	Not RIF
Lan et al 2019	Non-randomized	342 cycles of women ≥ 40 years with POR undergoing their first ART treatment in the study's clinic	8 IU/GH/day SC from the day the first leading follicle was 14 mm in diameter until the day of hCG	No treatment	Not RIF
Schoolcraf t et al. 1992	Prospective study in which patients served as their own controls	32 women with POR	4 IU GH/day IM simultaneosly with FSH until the day of hCG	No treatment	Not RIF
Du et al. 2016	Retrospective clinical trial	1114 women undergoing ART. BMI > 25 kg/m^2were excluded	4.5 IU GH/day SC for 5 days, beginning on the initial day of FSH administration	No treatment	Not RIF

HRT: hormone replacement therapy; RIF: recurrent implantation failure; GH: growth hormone; IVF: in-vitro fertilization; SC: subcutaneous; POR: poor ovary response; hCG: human chorionic gonadotropin; ART: assisted reproductive technologies; FSH: follicle stimulating hormone; BMI: body mass index.

3.4. Metanalysis of primary outcomes

CPR: GH administration was associated with higher rates of clinical pregnancy when compared with no intervention (OR: 4.97 CI 95% 2.05 to 12.05; 112 participants; 2 studies; I^2= 0% (Fig. 3*).*

Figure 3. Forest plot of clinical pregnancy rate Abbreviations: GH: Growth hormone CI: confidence interval



3.5. Metanalysis of secondary outcomes

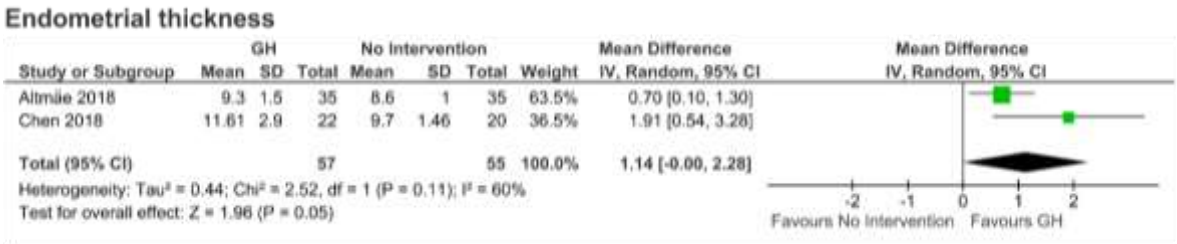
LBR: both studies reported LBR. GH administration was associated with higher rates of live birth when compared with no intervention (OR: 5.13 CI 95% 2.03 to 12.91; 112 participants; 2 studies; I^2 = 0%) (Fig. 4)

Figure 4: Forest plot of live birth rate. Abbreviations: GH: Growth hormone CI: confidence interval

Endometrial thickness: Both studies reported endometrial thickness as an outcome. GH administration was associated with a higher number in millimeters when endometrium was measured compared with no intervention (Mean

difference: 1.14 CI 95% -0.0 to 2.28; 112 participants; 2 studies; I^2 = 60%) (Fig. 5)

Figure 5: Forest plot of endometrial thickness. Abbreviations: GH: Growth hormone CI: confidence interval

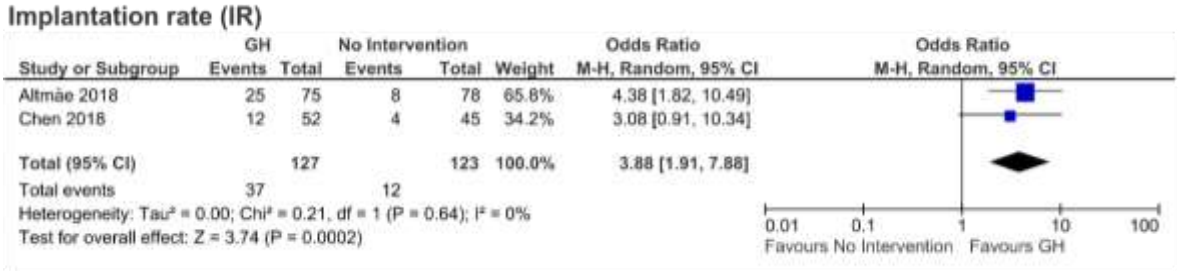


Number of embryos obtained: Both studies reported the number of embryos obtained as an outcome. There was no evidence of a difference between GH administration and no intervention (Mean difference: -0.25 CI 95% -1.12 to 0.61; 112 participants; 2 studies; I^2 = 0%) (Fig. 6)

Figure 6: Forest plot of numbers of embryos obtained. Abbreviations: GH: Growth hormone CI: confidence interval

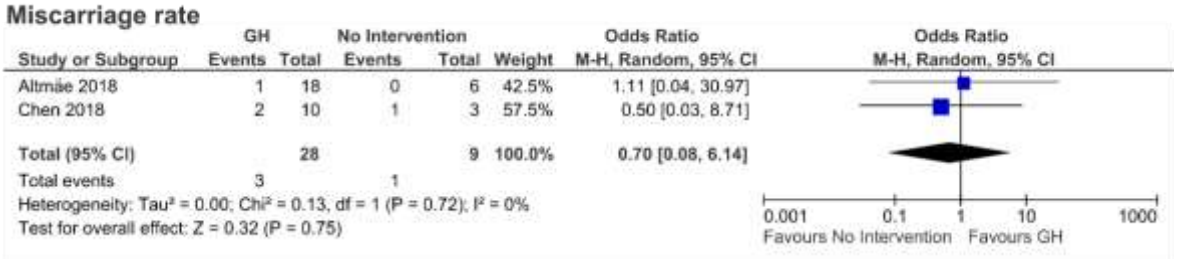
IR: Both studies reported the implantation rate as an outcome. GH administration was related to higher implantation rates when compared to no intervention (OR: 3.88 CI 95% 1.91 to 7.88; 112 participants; 250 transferred embryos; 2 studies; I^2 = 0%) (Fig. 7)

Figure 7: Forest plot of implantation rate. Abbreviations: GH: Growth hormone CI: confidence interval



MR: Both studies reported the miscarriage rate as an outcome. There was no evidence that GH administration was related to changes in miscarriage rates when compared to no intervention (OR: 0.70 CI 95% 0.08 to 6.14; 112 participants; 37 pregnant patients; 2 studies; I^2 = 0%) (Fig. 4)

Figure 8: Forest plot of miscarriage rate. Abbreviations: GH: Growth hormone CI: confidence interval



MPR: Neither of the studies provided MPR. However, Altmäe et al. showed data that enabled us to calculate information about MPR, having 6 multiple pregnancies out of 18 clinical pregnancies in the GH group (7.1%) and 2 multiples pregnancies out of 6 in the no intervention group (5.7%)

Adverse effects of GH treatment: none of the studies provided information about adverse effects, neither if they were present or absent, non what type of

adverse effects they search for, or even if they search for them.

Congenital abnormalities: none of the studies provided clear information about congenital abnormalities in live-born babies.

Table 4: Summary of metanalysis results

Dichotomic Outcomes	Number of Events				Effect measurement	CI 95%	I^2	GRADE quality
	GH (#/total)		No intervention (#/total)					
CPR	Altmäe 2018	18/35	Altmäe 2018	6/35	OR: 4.97	2.05-12.05	0%	Very low
	Chen 2018	10/22	Chen 2018	3/20				
LBR	Altmäe 2018	18/35	Altmäe 2018	6/35	OR: 5.13	2.03-12.91	0%	Very low
	Chen 2018	8/22	Chen 2018	2/20				
IR	Altmäe 2018	25/75	Altmäe 2018	8/78	OR: 3.88	1.91-7.88	0%	Very low
	Chen 2018	12/52	Chen 2018	4/45				
MR	Altmäe 2018	1/18	Altmäe 2018	0/6	OR: 0.70	0.08-6.14	0%	Very low
	Chen 2018	2/10	Chen 2018	1/3				
Continous Outcomes	Mean (SD)				Effect measurement	CI 95%	I^2	GRADE quality
	GH		No intervention					
Endometrial thickness	Altmäe 2018	9.3 (1.5)	Altmäe 2018	8.6 (1)	Mean difference: 1.14	-0.00-2.28	60%	Very low
	Chen 2018	11.61 (2.9)	Chen 2018	9.7 (1.46)				
Number of embryos obtained	Altmäe 2018	7.9 (2.2)	Altmäe 2018	8.2 (1.5)	Mean difference: -0.25	-1.12-0.61	0%	Very low
	Chen 2018	8.13 (5.46)	Chen 2018	7.35 (7.88)				

CPR: clinical pregnancy rate; LBR: live birth rate; IR: implantation rate; MR: miscarriage rate; GH: growth hormone; OR: odds ratio, CI: confidence interval; SD: standard deviation.

3.6. GRADE assessment

Table 5: Summary of findings and GRADE assessment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GH	No intervention	Relative (95% CI)	Absolute (95% CI)		
Clinical pregnancy												
2	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	28/57 (49.1%)	9/55 (16.4%)	**OR 4.97** (2.05 to 12.05)	**329 more per 1000** (from 123 more to 539 more)	⊕◯◯◯ VERY LOW	CRITICAL
Live birth rate												
2	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	26/57 (45.6%)	8/55 (14.5%)	**OR 5.13** (2.03 to 12.91)	**321 more per 1000** (from 111 more to 542 more)	⊕◯◯◯ VERY LOW	CRITICAL
Miscarriages rate												
2	randomised trials	serious [a]	not serious	serious [b]	serious [d]	none	3/28 (10.7%)	1/9 (11.1%)	**OR 0.70** (0.08 to 6.14)	**31 fewer per 1000** (from 101 fewer to 323 more)	⊕◯◯◯ VERY LOW	CRITICAL
Congenital abnormalities, Multiple pregnancy rate and GH related side effects - not reported outcomes												
-	-	-	-	-	-	-					-	CRITICAL
Implantation rate												
2	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	37/127 (29.1%)	12/123 (9.8%)	**OR 3.88** (1.91 to 7.88)	**198 more per 1000** (from 74 more to 362 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Number of embryos obtained												
2	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	57	55	-	MD **0.25 lower** (1.12 lower to 0.61 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
Endometrial thickness												
2	randomised trials	serious [a]	serious [e]	serious [b]	serious [c]	none	57	55	-	MD **1.14 higher** (0 to 2.28 higher)	⊕◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. Included RCTs did not mention any clear statement about their random sequence generation neither the allocation concealment.
b. Population was not consistently defined by included RCTs. Intervention was not provided by following a similar regime of administration and dose.
c. Limited sample sizes of included RCTs. Imprecise due to large confidence intervals.
d. Limited sample sizes of included RCTs. Imprecise due to large confidence intervals and low number of events.
e. Heterogeneity was calculated at 60%.

4. Discussion

This meta-analysis, including two trials shows that GH treatment in patients with RIF undergoing ART potentially improves reproductive outcomes such as clinical pregnancy and live birth rate without impacting the miscarriage rate. However, the overall quality of the available evidence is low.

The RCT by Altmäe et al. had some troubles with design, regarding the lack of clarity in the randomization process and allocation concealment, downgrading its GRADE qualification (54,55,56). They included patients from an oocyte-donation program, where the recipients were women with RIF diagnosis up to 51 years old, consistent with the American Society for Reproductive Medicine (ASRM) in oocyte-donation for women >50 years (58), however, arising the controversy of the increased obstetrical risk and low rate of success in ART associated with advanced maternal age (59,60,61). This study evaluates GH's effect on endometrial receptivity, since the recipients received the treatment, but none of the donors; proposing that GH might positively stimulate genes and pathways that otherwise would be dysregulated in the endometrium of women with RIF (52). Nevertheless, oocyte donation remains a sensitive topic, especially in Spain, where there has been an increasing cross-border migration of foreigner couples searching for oocyte donation programs (62,63). Still, in the study, they do not mention the patients' nationalities, which given the role of the embryo in implantation, could affect the reproductive outcomes. These observations indicate that the study population could be heterogeneous in demographic characteristics not mentioned by the authors. Despite those concerns, this article fulfilled the inclusion criteria for our review.

The second RCT by Chen et al. had more concerns regarding its methodological design since it did not explain anything about the randomization process, neither the allocation concealment. We could not contact the authors regarding their protocol or previously published versions of the article, stopping us from assessing selective reporting, granting it an unclear risk in this domain; all of that resulted in a significant downgrading in its quality. They included patients with RIF that met specific inclusion and exclusion criteria (tables I and II), enabling them to have a homogeneous study population. All the patients had follicular fluid collected and harvested for embryo collection for mRNA studies for steroidogenic acute regulatory protein (StAR) and GH receptor. That concords with findings in recent articles that stated that GH treatment improves the GH receptor expression, resulting in enhanced reproductive outcomes, including clinical pregnancy (64).

In terms of secondary outcomes, such as live-birth rate, endometrial thickness, and implantation rate, GH administration showed favorable results despite heterogeneous study population. Several systematic reviews regarding GH treatment in different types of patients and diagnoses, especially patients with poor prognosis such as POR, older women have also shown this improvement pattern (65,66,67,68,69) in agreement with our findings. Enabling us to believe that GH can have a potential beneficial effect on reproductive outcomes in patients that have failed previous cycles or that might have low chances from the first cycle in the light of current evidence.

We performed this systematic review in patients with RIF, although we could not use a set definition as inclusion criteria making heterogeneity an

expected issue in the analysis. We also encountered the differences between patients' baseline characteristics in both studies since one was in an oocyte donation program while the other involved transfers with proper embryos; this could have had an additional underlying effect because embryos and its quality also play an essential role in the implantation process. However, these differences can also be considered a result for this review, since the findings showed a consistent improvement in clinical pregnancy and live-birth rate, despite the study population's variation.

We were not able not obtain information from included studies regarding other outcomes mentioned in our protocol, preventing us from analyzing congenital abnormalities and multiple pregnancy rates. Neither, results related to GH's safety aspect, such as adverse effects (whether they were in the patient or pregnancy-related), caused by the treatment, unable us to fulfill the objective of describing efficacy and GH's safety co-intervention in RIF.

The major limitation we came across was the limited number of articles that could match the inclusion criteria. We narrowed to RCTs, hoping this specific scope would provide a better methodological design to analyze. Despite this, we realized that the studies' quality was not as adequate as expected, rated as "very low quality of evidence" in all the outcomes we selected for this review. For several reasons, as the lack of any clear statement about their random sequence generation, neither the allocation concealment, heterogeneity (even 60% in an outcome) in population, intervention regimen, and limited sample sizes with large confidence intervals and a low number of events (Table III). Due to the GRADE qualification of the articles included in this review, we concluded that although the

GH intervention may increase positive pregnancy-related outcomes, the evidence is uncertain, resulting in a weak recommendation opened to the clinician and patient's choices (55,56,70,71).

A critical affair to consider is that our literature searches not find another review of GH treatment in patients with RIF, and this review, although the first, does not provide a clear perspective or blueprint to implement this treatment as everyday clinical practice; due to the lack of actual evidence or studies regarding this diagnosis, that as mentioned before could be misdiagnosed (either under or overestimated) on account of an unclear consensus in its definition. It also leads us to recommend and underline the importance of addressing this population, which may be a minority, still, it is one with one of the highest impact deteriorate in life quality.

This review's results do not advocate routine use of GH as an adjunct in women with RIF, we encourage physicians to individualize each patient and their own needs and possible benefits from this co-intervention. However, they indicate a strong need to evaluate its role in enhancing endometrial receptivity, translate in better reproductive outcomes, in both clinical and basic science research. This need can be accomplished by designing and performing adequately powered RCTs, possibly multi-centered, using standardized criteria for defining unexplained RIF and using GH as the only co-intervention.

5. References

1. Ochoa-Bernal M, Fazleabas A. Physiologic Events of Embryo Implantation and Decidualization in Human and Non-Human Primates. Int. J. Mol. Sci. 2020;21(6):1973-1994.

2. Robins JC. Implantation: Trophoblast-Endometrial Interactions. Semin Reprod Med. 2016;34(1):3-4.

3. Kim S, Kim J. A Review of Mechanisms of Implantation. Dev Reprod 2017; 21(4):351-359.

4. Vitiello D, Patrizio P. Implantation and early embryonic development: implications for pregnancy. Semin Perinatol. 2007;31(4):204-207.

5. Teh WT, McBain J, Rogers P. What is the contribution of embryo-endometrial asynchrony to implantation failure? J Assist Reprod Genet. 2016;33(11):1419-1430.

6. Sebastian-León P, Garrido N, Remohí J, Pellicer A, Diaz-Gimeno P. Asynchronous and pathological windows of implantation: Two causes of recurrent implantation failure. Hum Reprod. 2018;33:626–635.

7. Coughlan C, Ledger W, Wang Q, Liu F, Demirol A, Gurgan T, Cutting R, Ong R, Sallam H, Li TC. Recurrent implantation failure: definition and management. Reprod BioMed Online. 2014;28(1):14–38.

8. Zeyneloglu HB, Onalan G. Remedies for recurrent implantation failure. Semin Reprod Med. 2014;32(4):297–305.

9. Rinehart J. Recurrent implantation failure: definition. J Assist Reprod Genet. 2007;24(7):284-287.

10. Zohni KM, Gat I, Librach C. Recurrent implantation failure: a comprehensive review. Minerva Ginecol. 2016;68(6):653-667.

11. Somigliana E, Vigano P, Busnelli A, Paffoni A, Vegetti W, Vercellini P. Repeated implantation failure at the crossroad between statistics, clinics and over-diagnosis. Reprod Biomed Online. 2018;36(1):32-38.

12. Thornhill AR, deDie-Smulders CE, Geraedts JP, Harper JC, Harton GL, Lavery SA, Moutou C, Robinson MD, Schmutzler AG, Scriven PN et al. ESHRE PGD Consortium 'Best practice guidelines for clinical preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS)'. Hum Reprod 2005;20:35 –48.

13. Bashiri A, Halper KI, Orvieto R. Recurrent Implantation Failure-update overview on etiology, diagnosis, treatment and future directions. Reprod Biol Endocrinol. 2018;16(1):121-139.

14. Kliman HJ, Frankfurter D. Clinical approach to recurrent implantation failure: evidence-based evaluation of the endometrium. Fertil Steril. 2019;111(4):618-628.

15. Magdi Y, El-Damen A, Fathi AM, et al. Revisiting the management of recurrent implantation failure through freeze-all policy. Fertil Steril. 2017;108(1):72-77.

16. Moustafa S, Young SL. Diagnostic and therapeutic options in recurrent implantation failure [version 1; peer review: 2 approved]. F1000Research 2020; 9(F1000 Faculty Rev):208-217.

17. Altmäe S, Reimand JR, Hovatta O, Zhang P, Kere J, Laisk T, Saare M, Peters M, Vilo J, Stavreus-Evers A, et al. Research resource: interactome of

human embryo implantation: identification of gene expression pathways, regulation, and integrated regulatory networks. Mol Endocrinol. 2012;26:203–217.

18. Lessey B, Young S. What exactly is endometrial receptivity? Fertil Steril. 2019;111(4):611-617.

19. Dvořan M, Vodička J, Dostál J, Hajdúch M, Džubák P, Pešková M, Pilka R. Implantation and diagnostics of endometrial receptivity. Implantace a diagnostika receptivity endometria. Ceska Gynekol. 2018;83(4):291-298.

20. Miravet-Valenciano JA, Rincon-Bertolin A, Vilella F, Simon C. Understanding and improving endometrial receptivity. Curr Opin Obstet Gynecol. 2015;27(3):187-192.

21. Paulson RJ. Introduction: Endometrial receptivity: evaluation, induction and inhibition. Fertil Steril. 2019;111(4):609-610.

22. Cailleau J, Vermeire S, Verhoeven G. Independent control of the production of insulin-like growth factor I and its binding protein by cultured testicular cells. Mol Cell Endocrinol. 1990;69:79–89.

23. Altmäe S, Aghajanova L. Growth Hormone and Endometrial Receptivity. Front Endocrinol (Lausanne). 2019;10:653-664.

24. Liu FT, Wu Z, Yan J, Norman RJ, Li R. The Potential Role of Growth Hormone on the Endometrium in Assisted Reproductive Technology. Front Endocrinol (Lausanne). 2020;11:49-57.

25. Cui N, Li AM, Luo ZY, Zhao SM, Xu YM, Zhang J, Yang AM, Wang LL, Hao GM, Gao BL. Effects of growth hormone on pregnancy rates of patients with thin endometrium [published correction appears in J Endocrinol Invest. 2018 Aug 20;:]. J Endocrinol Invest. 2019;42(1):27-35.

26. Sbracia M, Scarpellini F, Poverini R, Alò PL, Rossi G, Di Tondo U. Immunohistochemical localization of the growth hormone in human endometrium and decidua. Am J Reprod Immunol. 2004;51:112–116

27. Ferrara N. Vascular Endothelial Growth Factor. Arterioscler Thromb Vasc Biol. 2009;29(6):789-791.

28. Korompelis P, Piperi C, Adamopoulos C, Dalagiorgou G, Korkolopoulou P, Sepsa A, Antsaklis A, Papavassiliou AG. Expression of vascular endothelial factor-A, gelatinases (MMP-2, MMP-9) and TIMP-1 in uterine leiomyomas. Clin Chem Lab Med. 2015;53(9):1415-1424.

29. Popovici RM, Irwin JC, Giaccia AJ, Giudice LC. Hypoxia and cAMP stimulate vascular endothelial growth factor (VEGF) in human endometrial stromal cells: potential relevance to menstruation and endometrial regeneration. J Clin Endocrinol Metab. 1999;84(6):2245-2248.

30. Sun ZG, Lian F, Jia Q, Sun JL, Li TT, Guo Y, Zhang JW, Zhang N, Liu H, Wang LH. Effects of Er'zhi Tiangui Granule on sequential expressions of integrin β 3 and its ligand osteopontin in mouse endometrium during controlled ovarian hyperstimulation. Chin J Integr Med. 2012;18(11):846-849

31. Tei, C, Maruyama T, Kuji N, Miyazaki T, Mikami M, Yoshimura Y. Reduced Expression of αvβ3 Integrin in the Endometrium of Unexplained Infertility Patients with Recurrent IVF-ET Failures: Improvement by Danazol Treatment. J Assist Reprod Genet. 2003;20:13–20

32. Lessey BA, Castelbaum AJ. Integrins and implantation in the human. Rev Endocr Metab Disord. 2002;3(2):107-117.

33. Kaneko Y, Day ML, Murphy CR. Integrin β3 in rat blastocysts and epithelial

cells is essential for implantation in vitro: studies with Ishikawa cells and small interfering RNA transfection. Hum Reprod. 2011;26(7):1665-1674.

34. Taketani T, Yamagata Y, Takasaki A, Matsuoka A, Tamura H, Sugino N. Effects of growth hormone and insulin-like growth factor 1 on progesterone production in human luteinized granulosa cells. Fertil Steril. 2008;90:744–748.

35. Schams D, Berisha B, Kosmann M, Einspanier R, Amselgruber WM. Possible role of growth hormone, IGFs, and IGF-binding proteins in the regulation of ovarian function in large farm animals. Domest Anim Endocrinol. 1999;17:279–285

36. Poretsky L, Cataldo NA, Rosenwaks Z, Giudice LC. The insulin-related ovarian regulatory systemin health and disease. Endocr Rev. 1999;20:535–82

37. Eftekhar M, Aflatoonian A, Mohammadian F, Eftekhar T. Adjuvant growth hormone therapy in antagonist protocol in poor responders undergoing assisted reproductive technology. Arch Gynecol Obstet. 2013;287:1017–1021.

38. Dakhly DMR, Bayoumi YA, Gad Allah SH. Which is the best IVF/ICSI protocol to be used in poor responders receiving growth hormone as an adjuvant treatment? A prospective randomized trial. Gynecol Endocrinol. 2016;32:116–119.

39. Kucuk T, Kozinoglu H, Kaba A. Growth hormone co-treatment within a GnRH agonist long protocol in patients with poor ovarian response: a prospective, randomized, clinical trial. J Assist Reprod Genet. 2008;25:123–127.

40. Dakhly DMR, Bassiouny YA, Bayoumi YA, Hassan MA, Gouda HM, Hassan AA. The addition of growth hormone adjuvant therapy to the long down regulation protocol in poor responders undergoing in vitro fertilization: Randomized control trial. Eur J Obstet Gynecol Reprod Biol. 2018;228:161–165.

41. Wu H, Li L, Li M, Yuan H. Effect of growth hormone on the endometrial and endometrial blood flow in forzen thawed embryo tranfer. J Reprod Med. 2013;12:914-917.

42. Yu H, Gao S, Tang H, Chen H, Deng Z, Yang L, et al. Growth hormone intrauterine perfusion combined with replacement cycle in the treatment of non-response thin endometrium: report of 5 cases. Int J Clin Exp Med. 2016;9:11982-11989.

43. Yang JY, Li H, Lu N, Li L, Sun XX. Influence of growth hormone supplementation in patients with thin endometrium undergoing frozen embryo transfer. Reprod Dev Med. 2019;3:49-53.

44. Lan KC, Lin PY, Chang YC, Chen YJ, Tsai YR, Mohamed ISI, Kang HY. Growth hormone supplementation may improve the pregnancy rate and endometrial receptivity among women aged more than 40 years undergoing in vitro fertilization. Biomed J. 2019;42(6):411-416.

45. Choe SA, Kim MJ, Lee HJ, Kim J, Chang EM, Kim JW, Park HM, Lyu SW, Lee WS, Yoon TK et al. Increased proportion of mature oocytes with sustained-release growth hormone treatment in poor responders: a prospective randomized controlled study. Arch Gynecol Obstet. 2018;297:791-796.

46. Coughlan C, Walters S, Ledger W, Li TC. A comparison of psychological stress among women with and without reproductive failure. Int J Gynaecol Obstet. 2014;124(2):143-147.

47. Gameiro S, Boivin J, Peronace L, Verhaak CM. Why do patients discontinue fertility treatment? A systematic review of reasons and predictors of discontinuation in fertility treatment. Hum Reprod Update. 2012;18(6):652-669.

48. Gameiro S, Verhaak CM, Kremer JA, Boivin J. Why we should talk about compliance with assisted reproductive technologies (ART): a systematic review and meta-analysis of ART compliance rates. Hum Reprod Update. 2013;19(2):124-135.

49. Busnelli A, Reschini M, Cardellicchio L, Vegetti W, Somigliana E, Vercellini P. How common is real repeated implantation failure? An indirect estimate of the prevalence. Reprod Biomed Online. 2020;40(1):91-97.

50. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

51. Andrews JC, Schünemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation - Determinants of a recommendation's direction and strength. Journal of Clinical Epidemiology. 2013; 66 (7): 726–735

52. Santesso N, Glenton C, Dahm P, Garner P, Akl EA, Alper B, Brignardello-Petersen R, Carrasco-Labra A, De Beer H, Hultcrantz M, et al; GRADE Working Group. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. J Clin Epidemiol. 2020;119:126-135.

53. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-926.

54. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Open Med 2009;3(3); 123-130

55. Altmäe S, Mendoza-Tesarik R, Mendoza C, Mendoza N, Cucinelli F, Tesarik J. Effect of Growth Hormone on Uterine Receptivity in Women With Repeated Implantation Failure in an Oocyte Donation Program: A Randomized Controlled Trial. Journal of the Endocrine Society. 2018;2(1):96-105.

56. Chen Y, Liu F, Nong Y, Ruan J, Guo Q, Luo M et al. Clinical efficacy and mechanism of growth hormone action in patients experiencing repeat implantation failure. Canadian Journal of Physiology and Pharmacology. 2018;96(9):929-932.

57. CORRIGENDUM FOR “Effect of Growth Hormone on Uterine Receptivity in Women With Repeated Implantation Failure in an Oocyte Donation Program: A Randomized Controlled Trial”. Journal of the Endocrine Society. 2018;2(2):133-133.

58. Ethics Committee of the American Society for Reproductive Medicine. Oocyte or embryo donation to women of advanced age: a committee opinion. Fertil Steril. 2013;100(2):337-340.

59. Ethics Committee of the American Society for Reproductive Medicine. Fertility treatment when the prognosis is very poor or futile: an Ethics Committee opinion. Fertil Steril. 2019;111(4):659-663.

60. MacArthur T, Bachmann G, Ayers C. Menopausal women requesting egg/embryo donation: examining health screening guidelines for assisted reproductive technology. Menopause. 2016;23(7):799-802.

61. Somigliana E, Paffoni A, Busnelli A, Filippi F, Pagliardini L, Vigano P,

Vercellini P. Age-related infertility and unexplained infertility: an intricate clinical dilemma. Hum Reprod. 2016;31(7):1390-1396.

62. Nygren K, Adamson D, Zegers-Hochschild F, de Mouzon J; International Committee Monitoring Assisted Reproductive Technologies. Cross-border fertility care--International Committee Monitoring Assisted Reproductive Technologies global survey: 2006 data and estimates. Fertil Steril. 2010;94(1):e4-e10.

63. Madero S, Gameiro S, García D, Cirera D, Vassena R, Rodríguez A. Quality of life, anxiety and depression of German, Italian and French couples undergoing cross-border oocyte donation in Spain. Hum Reprod. 2017;32(9):1862-1870.

64. Regan SLP, Knight PG, Yovich JL, Arfuso F, Dharmarajan A. Growth hormone during in vitro fertilization in older women modulates the density of receptors in granulosa cells, with improved pregnancy outcomes. Fertil Steril. 2018;110(7):1298-1310

65. Yu X, Ruan J, He LP, Hu W, Xu Q, Tang J, Jiang J, Han J, Peng YF. Efficacy of growth hormone supplementation with gonadotrophins in vitro fertilization for poor ovarian responders: an updated meta-analysis. Int J Clin Exp Med. 2015;8(4):4954-67.

66. Hart RJ. Use of Growth Hormone in the IVF Treatment of Women With Poor Ovarian Reserve. Front Endocrinol (Lausanne). 2019;10:500-507.

67. Hart RJ, Rombauts L, Norman RJ. Growth hormone in IVF cycles: any hope? Curr Opin Obstet Gynecol. 2017;29(3):119-125.

68. Duffy J, Ahmad G, Mohiyiddeen L, Nardo L, Watson A. Growth hormone for in vitro fertilization. Cochrane Database of Systematic Reviews. 2010.

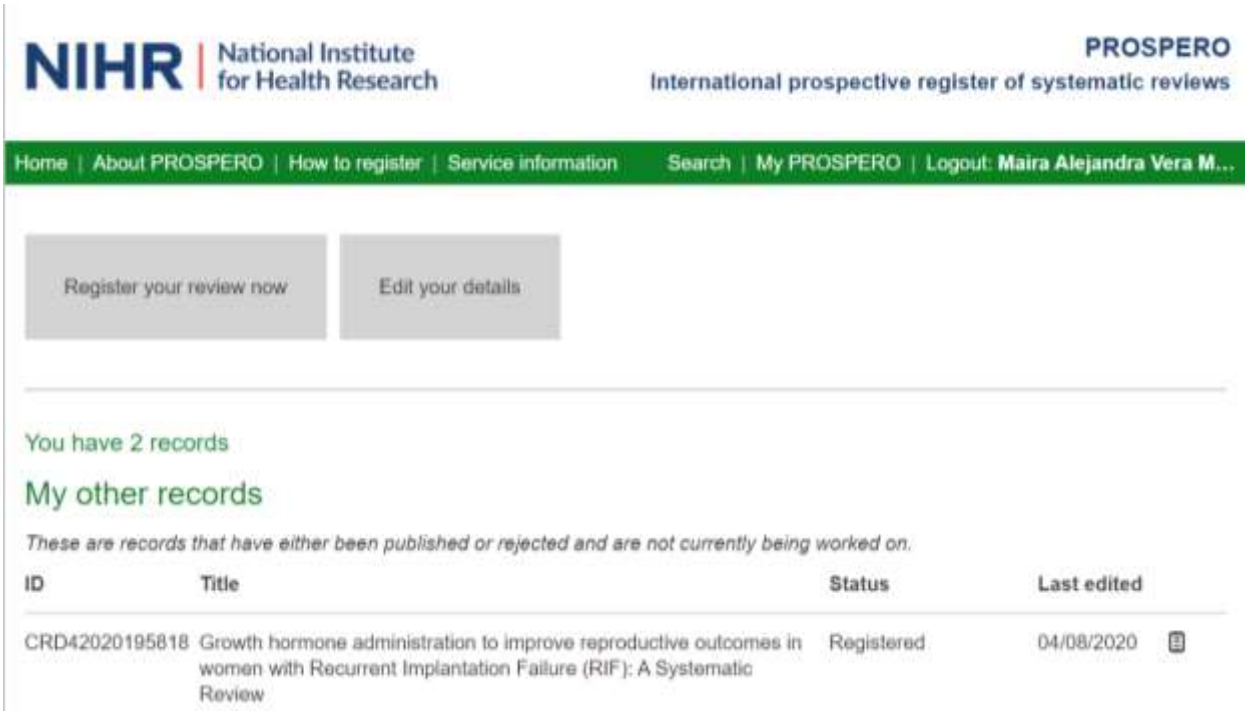
69. Zhang Y, Zhang C, Shu J, Guo J, Chang HM, Leung PCK, Sheng JZ, Huang

H. Adjuvant treatment strategies in ovarian stimulation for poor responders undergoing IVF: a systematic review and network meta-analysis. Hum Reprod Update. 2020;26(2):247-263.

70. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. What is "quality of evidence" and why is it important to clinicians? BMJ. 2008;336(7651):995-998.

71. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, Schünemann HJ; GRADE Working Group. Going from evidence to recommendations. BMJ. 2008;336(7652):1049-1051.

6. Anexo



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CRD42020195818	Growth hormone administration to improve reproductive outcomes in women with Recurrent Implantation Failure (RIF): A Systematic Review	Registered	04/08/2020