Growth Hormone Supplementation in the Luteal Phase Before Microdose GnRH Agonist Flare Protocol for In Vitro Fertilization

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Abstract

Objective: Growth hormone (GH) acts in both early and late follicular development to stimulate the proliferation and differentiation of granulosa cells and to increase the production of estradiol in animal and human ovaries. Investigators have therefore explored GH supplementation to improve outcomes in women undergoing in vitro fertilization, with the greatest interest in women with diminished ovarian reserve. Recent meta-analyses indicate that GH supplementation can be beneficial for poor responders undergoing IVF. In most studies, GH has been given concomitantly with gonadotropins during the follicular phase; this may not be optimal, since follicular recruitment begins during the preceding luteal phase. We therefore wished to examine the effect of GH supplementation in the luteal phase before controlled ovarian stimulation (COH) with a microdose GnRH agonist flare (MDF) protocol in women undergoing in vitro fertilization.

Methods: We performed a retrospective matched case–control study of patients undergoing treatment at a private IVF facility between June 2012 and July 2013. Patients identified as poor responders to COH were offered adjuvant GH treatment as part of their ovarian stimulation regimen. The patients in the experimental group chose to take GH, 3.33 mg daily by subcutaneous injection for 14 days, before starting COH. All patients had an MDF stimulation protocol using 450 IU of follicle stimulating hormone (FSH) daily.

Results: A total of 42 women were included in the study. There were 14 women in the experimental group (GH) and 28 controls (C) matched for age, BMI, and day 3 FSH level. There was no difference between the groups in clinical pregnancy rate (GH = 29%, C = 32%, *P* = 0.99), number of mature oocytes retrieved (GH = 2.5, C = 5.0, *P* = 0.13), cycle cancellation rate (GH = 21%, C = 14%, *P* = 0.88), duration of COH (GH = 10.1, C = 10.1, *P* = 0.93), or mean peak estradiol level (GH = 4174 pmol/L, C = 5105 pmol/L, *P* = 0.44).

Conclusion: The administration of growth hormone during the luteal phase before a microdose GnRH agonist flare protocol for in vitro fertilization did not improve outcomes in "poor responder" patients.

Key Words: Growth hormone, in vitro fertilization, microdose GnRH agonist flare, poor responder

Competing Interests: None declared.

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Résumé

Objectif : L'hormone de croissance (GH) agit pendant le développement folliculaire tant précoce que tardif pour stimuler la prolifération et la différenciation des cellules de la granulosa, ainsi que pour accroître la production d'estradiol par les ovaires chez l'animal et l'homme. Les chercheurs se sont donc penchés sur le recours à la supplémentation en GH pour améliorer les issues chez les femmes qui font appel à la fécondation *in vitro*, tout en portant une attention particulière aux femmes qui présentent une réserve ovarienne amoindrie. De récentes méta-analyses indiquent que la supplémentation en GH peut être bénéfique pour les femmes qui réagissent mal à la FIV. Dans la plupart des études, on administre de la GH de façon concomitante avec des gonadotrophines pendant la phase folliculaire; cette façon de faire pourrait ne pas être optimale, puisque le recrutement folliculaire débute au cours de la phase lutéale qui précède. Nous avons donc souhaité examiner l'effet de la supplémentation en GH pendant la phase lutéale, avant la tenue d'une stimulation ovarienne contrôlée (SOC) au moyen d'un « protocole de poussée » faisant appel à une microdose d'agoniste de la GnRH (MDF), chez des femmes qui font l'objet d'une fécondation *in vitro*.

Méthodes : Nous avons mené une étude cas-témoins appariés rétrospective se penchant sur des patientes qui ont fait l'objet d'un traitement au sein d'un établissement privé de FIV entre juin 2012 et juillet 2013. Les patientes identifiées comme réagissant mal à la SOC se sont vu offrir un traitement adjuvant à la GH dans le cadre de leur schéma thérapeutique de stimulation ovarienne. Les patientes du groupe expérimental ont choisi de recevoir de la GH, à raison de 3,33 mg par jour sous forme d'injection sous-cutanée pendant 14 jours, avant le début de la SOC. Toutes les patientes ont fait l'objet d'un protocole de stimulation MDF faisant appel à 450 UI d'hormone folliculostimulante (FSH) par jour.

Résultats : Au total, 42 femmes ont participé à l'étude. Le groupe expérimental (GH) comptait 14 femmes et le groupe témoin (C) comptait 28 femmes appariées en fonction de l'âge, de l'IMC et du taux de FSH au jour 3. Aucune différence n'a été constatée entre les groupes en matière de taux de grossesse clinique (GH = 29 %, C = 32 %, P = 0,99), de nombre d'ovocytes matures récupérés

(GH = 2,5, C = 5,0, P = 0,13), de taux d'annulation de cycle (GH = 21 %, C = 14 %, P = 0,88), de durée de la SOC (GH = 10,1, C = 10,1, P = 0,93) ou de niveau moyen du pic d'estradiol (GH = 4 174 pmol/l, C = 5 105 pmol/l, P = 0,44).

Conclusion : L'administration d'hormone de croissance pendant la phase lutéale, avant la mise en œuvre d'un « protocole de poussée » faisant appel à une microdose d'agoniste de la GnRH aux fins de la fécondation *in vitro*, n'a pas permis d'améliorer les issues obtenues par les patientes « réagissant mal » à la SOC.

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INTRODUCTION

In women undergoing in vitro fertilization, controlled ovarian stimulation is used to promote a multi-follicular response and thereby maximize each woman's odds of generating at least one developmentally competent oocyte. Growth hormone, a pituitary peptide, stimulates proliferation and differentiation of granulosa cells,[1,2] and increases the production of estradiol in animal and human ovaries.[1,3–5] It is believed to activate granulosa cells directly by binding to the growth hormone receptor, and indirectly by stimulating the production of insulin-like growth factor I in ovarian or other tissues.[6–8]

Both human and animal studies have suggested a role for GH in folliculogenesis. In rhesus macaque ovaries, GHR is expressed in the cumulus-oocyte-complex; administration of recombinant human GH increases cumulus expansion and development of embryos to the nine- to 16-cell stage, consistent with a stimulating effect of GH on oocyte maturation.[9,10] In humans, GHR mRNA and protein are highly expressed in granulosa cells, ovarian stromal cells, and oocytes.[11,12] GHR expression in the corpus luteum may indicate a role for GH in the luteal phase.[13,14] Intrafollicular GH levels have been demonstrated to vary between human follicles, and higher GH concentrations have been associated with normal embryo morphology and vigorous cell growth during assisted reproduction procedures.[15] Together, these findings suggest that GH participates in follicular growth and development of oocytes and early embryos through several distinct cell types and at multiple steps. Investigators have therefore explored the potential for GH supplementation to improve outcomes in women undergoing IVF, most commonly in those with a history of poor response to ovarian stimulation ("poor responders").[2]

In this study we assessed the effects of treatment with growth hormone in the luteal phase before COH with a microdose GnRH agonist flare (MDF) protocol in women undergoing in vitro fertilization.

ABBREVIATIONS

COH	controlled ovarian stimulation
FSH	follicle stimulating hormone
GH	growth hormone
GHR	growth hormone receptor
POR	poor ovarian response

METHODS

We performed a retrospective, matched case–control study of patients undergoing in vitro fertilization at a private IVF facility between June 2012 and July 2013. Patients identified as poor responders to COH were offered adjuvant GH treatment as part of their ovarian stimulation regimen. All women who received GH (the experimental group) met the Bologna classification for poor ovarian response, having had two prior episodes of POR or at least two of the following: advanced maternal age or risk factors for POR, previous poor response to COH, or abnormal ovarian reserve testing.[5] The experimental group comprised women who elected to have GH treatment before COH; they received daily subcutaneous injections of 3.33 mg of GH (Saizen; EMD Serono, Mississauga, ON) for 14 days before beginning injections of FSH (Figure 1). The control group subjects were women undergoing contemporaneous IVF cycles who were not receiving GH; they were matched for age, day 3 FSH levels, and BMI. All patients had controlled ovarian stimulation using a microdose GnRH agonist flare protocol; this involved 14–35 days of a combined oral contraceptive preparation, followed three days later by twice daily subcutaneous injections of 40 μg of leuprolide acetate (Lupron; Abbvie Corp., Saint-Laurent, QC) and daily subcutaneous injections of 450 IU of recombinant FSH (r-FSH) beginning on the third day of withdrawal bleeding.

All subjects had undergone routine screening for thyroid dysfunction, glucose intolerance (if indicated), uterine abnormalities, and respiratory or cardiovascular dysfunction before beginning in vitro fertilization treatment. Ovarian follicular growth was monitored by serial transvaginal ultrasound and serum estradiol measurement. When two or more follicles reached a mean of 17 mm in diameter, 10 000 IU of human chorionic gonadotropic was administered subcutaneously to trigger final oocyte maturation. Transvaginal oocyte retrieval was performed 36 hours after human chorionic gonadotropic administration, and standard fertilization in vitro or intracytoplasmic sperm injection was performed as appropriate. Luteal phase support was given in the form of micronized vaginal progesterone. Clinical pregnancy was

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