

The conventional doses of human chorionic gonadotropins may not always be sufficient to induce ovulation in all women: A reappraisal

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Summary

Background: Failure of ovulation has occasionally been reported following the administration of conventionally recommended doses of exogenous human chorionic gonadotropins.

Case: A 25-year-old nulliparous woman with polycystic ovary syndrome underwent ovulation induction for primary infertility. Following successful ovarian stimulation, she failed to ovulate during two consecutive cycles in response to human chorionic gonadotropin doses of 5,000 and 10,000 IU. When challenged with a higher than conventional dose (15,000 IU) on the third cycle, she ovulated and conceived.

Conclusion: Conventional doses of exogenous human chorionic gonadotropins occasionally fail to complete the ovulatory process in some women. Women with polycystic ovary syndrome appear to be particularly susceptible. Routine documentation of ovulation and individualization of the dose of exogenous human chorionic gonadotropins could therefore prove to be useful in some of these women in order to achieve the best treatment outcome.

Key words: Ovulation induction; Polycystic ovary syndrome; Human chorionic gonadotropins.

Introduction

Human chorionic gonadotropins (hCG) have been successfully used to mimic the LH surge in women by virtue of their LH-like activity and their slower plasma metabolic clearance rate. A single intramuscular injection consisting of 5,000 to 10,000 I.U. is conventionally utilized for the medical induction of ovulation in women. Apparently, not all women respond similarly to the above-suggested doses of gonadotropins. We present a woman with polycystic ovary syndrome (PCOS) in whom conventional doses of hCG failed to trigger ovulation despite optimal follicular response, and in whom higher doses were required to complete the ovulatory process.

Case Report

A 25-year-old woman with polycystic ovary syndrome was evaluated for a two-year history of primary infertility. The clinical presentation consisted of oligomenorrhea, facial/peripheral hirsutism, and acne. Ultrasound of the ovaries showed increased volume, dense stroma and numerous peripheral cysts. The hormonal profile was unremarkable and consisted of the following: FSH 3.7 mIU/ml, LH 4.5 mIU/ml, dehydroepiandrosterone sulfate (DHEAS) 2802 ng/ml, testosterone 49 ng/ml, TSH 2.26 µU/ml, triiodothyronine (T3) 1.26 ng/ml, thyroxine (T4) 5.28 µg/dl, and prolactin 11.5 ng/ml. Fasting glucose levels were 87 mg/dl. The woman had no evidence of glucose intolerance and had a BMI of 33.4 kg/m². The hysterosalpingogram revealed

bilateral tubal spillage and a normal uterine cavity. The husband's semen analysis showed sperm parameters within normal range. The patient had previously demonstrated unovulatory cycles and absence of follicular development to clomiphene citrate therapy.

The decision was then made to initiate ovarian stimulation utilizing low-doses of urinary follitropins (uFSH; Metrodin, Serono; 75 I.U. IM daily) in a step-up protocol. A total of three consecutive cycles was undertaken before the achievement of conception; the stimulation characteristics of which are described in Table 1. Follicular development was observed to be satisfactory in all three cycles, and consisted of three pre-ovulatory follicles (≥ 16 mm in diameter each) following nine days of treatment. Human chorionic gonadotropins (hCG; Profasi, Serono; 5,000 I.U./ampoule) were then given at this particular time of each cycle to trigger ovulation. Estradiol levels on the day of hCG were 330, 420 and 370 pg/ml, respectively. During the first treatment cycle, 5,000 I.U. of hCG were administered by the intramuscular route. Serum progesterone levels taken twice during the luteal phase remained low (< 3 ng/ml). The patient missed her periods and had a negative serum pregnancy test. During the second treatment cycle, 10,000 I.U. were given. Ultrasound monitoring performed 48 hours following the injection failed to demonstrate any signs of ovulation, and mid-luteal blood samples taken twice did not show any significant rise in progesterone levels (< 3 ng/ml). The cycle menses were delayed again. During the third treatment cycle, the hCG dose was increased by one ampoule above conventionally accepted doses, up to 15,000 I.U. Ultrasound examination this time confirmed follicular rupture, and mid-luteal progesterone levels showed a significant serum rise (> 20 ng/ml). The patient missed her periods and was found to be pregnant. She carried to term and was delivered vaginally of a live female newborn weighing 2,800 g at 38 weeks of gestation.

Revised manuscript accepted for publication June 10, 2001

Table 1. — *The stimulation characteristics of three treatment cycles in a woman with polycystic ovary syndrome.*

	Cycle 1	Cycle 2	Cycle 3
Total number of ampoules used (amps)	11	11	11
Total days of stimulation (days)	9	9	9
Serum estradiol levels on day of hCG (pg/ml)	330	420	370
Total follicles \geq 16 mm	3	3	3
hCG dose administered (IU)	5,000	10,000	15,000
Serum progesterone levels, midluteal (ng/ml)	< 3	< 3	> 20
Serum pregnancy test	Negative	Negative	Positive

Discussion

The mid-cycle LH gonadotropin surge is the major triggering factor for the dynamics of ovulation. Rising serum LH levels induce a series of events at the level of the oocytes and the follicular cells, resulting in alterations to the local and peripheral hormonal milieu. These physiological changes play a prominent role in the maturation of oocytes and the completion of the ovulatory process. In addition to their LH-like activity at the follicular level, human chorionic gonadotropins possess a slower plasma metabolic clearance rate than LH. This pharmacokinetic property offers the benefit of inducing ovulation utilizing exogenous hCG by use of a single dose administration approach. Unfortunately, the minimal duration of gonadotropin exposure required to initiate the oocyte nuclear events and the follicular ovulatory process, remains poorly defined and largely unexplored. One study demonstrated that human metaphase II oocytes could be recovered as early as 28 hours after the onset of the LH surge [1]. Another study suggested that the minimal exposure duration time to LH activity required for reinitiating meiosis can be as little as 14 to 18 hours [2]. Similarly, little is also known about the minimal serum amplitude levels of LH needed to initiate these cellular events. Studies in rodents have shown that only 5% of the normal LH surge is necessary to initiate oocyte maturation, and that more than 85% of peak LH levels are needed to activate actual ovulation [3]. These findings suggest that significantly higher serum gonadotropin levels are required to trigger the follicular ovulatory process, while much lower serum levels are sufficient to initiate the oocyte meiotic events. In other words, factors that interfere with proper kinetics following the intramuscular administration of hCG, could potentially impair proper ovulatory function and hence adversely affect treatment outcome.

The intramuscular doses of hCG widely accepted and traditionally utilized for the induction of ovulation in women have been conceived to be 5,000 and 10,000 I.U. given as a single injection. These doses lead to the completion of the ovulatory events 36 to 40 hours following administration. The case presented in this report failed nonetheless to follow the predicted course of events, and suggests that not all women ovulate uniformly in response to the conventionally accepted doses of hCG. A search for

confounding variables that could potentially interfere with adequate serum gonadotropin levels or their proper action on follicular cells, may therefore be warranted to improve the reproductive outcome in some women.

Increased body fat composition commonly occurs in women with PCOS. Hamilton-Fairley *et al.* demonstrated that significantly more ovulatory cycles occurred in these women after standard gonadotropin stimulation when they were less obese [4]. The mechanisms involved in obesity and which affect the dose requirements of exogenous gonadotropins and the outcome of treatment remain nevertheless unclear. Three possible explanations may be advanced: (I) Poor distribution of the hCG in the different body compartments following intramuscular injection occurs in the presence of altered fat to lean body weight ratio in obese women. Suboptimal tissue and follicular levels could subsequently become insufficient to complete the ovulatory process. (II) A shallow intramuscular injection can also result in low serum and tissue gonadotropin levels. A thick subcutaneous fat layer could potentially interfere with proper deposition of the drug into the muscular tissue, leading to poor absorption kinetics. (III) Altered tissue response to the gonadotropin action has also been suggested to derive from the abnormal hormonal profile associated with PCOS. Hyperinsulinemia and/or reduced tissue sensitivity to insulin were shown to play a role in reducing the biological activity of gonadotropins in tissues. Long-term dieting causing a reduction in fasting and glucose-stimulated insulin levels, for example, was found to be associated with significant improvement in ovarian function [5]. Such effect was independent of the serum concentration of gonadotropins. On the other hand, insulin-sensitizing agents have lately been utilized to improve the ovulatory performance of clomiphene citrate-resistant women with PCOS [6].

In conclusion, some women fail to ovulate in response to the conventionally accepted doses of hCG (5,000 and 10,000 I.U.) given as a single intramuscular injection. Women with PCOS appear to be more susceptible than others as some may express an altered tissue response to exogenous gonadotropins as a result of an abnormal hormonal profile and/or altered drug pharmacokinetics due to body habitus. We therefore find it useful to perform routine documentation of ovulation in women with PCOS on their first cycle of follicular stimulation. In some of these women, the dose of human chorionic gonadotropins may have to be individualized accordingly in order to ensure proper ovulation and to meet the desired treatment benefits. Prospective randomized controlled studies are needed however to confirm the benefits of such approach.

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VIII World Congress on Endometriosis

organized by the

American Society for Reproductive Medicine

San Diego, California

February 24-27, 2002

NEEDS ASSESSMENT AND MEETING DESCRIPTION

Endometriosis is a common gynecologic disorder which is often responsible for severe and debilitating symptoms. Despite considerable basic and clinical research, there are many unanswered questions regarding the pathogenesis, pathophysiology, and clinical management of the disease. The overall objective of this World Congress is to provide a comprehensive overview of the biology and treatment of endometriosis. Health care practitioners who provide care to women with endometriosis need to have current information about endometriosis.

World recognized scientists and experts in the field of endometriosis research and patient management will participate in the Congress.

Topics will include the genetics of endometriosis, new drug development, in vitro and animal models of endometriosis, immunologic aspects of endometriosis, and treatment of endometriosis-related infertility and pelvic pain. Debates will discuss the relationship of endometriosis and infertility, and the treatment of mild endometriosis.

The program also will include oral and poster presentations. Meritorious abstracts submitted specifically for the Congress will be selected by the Program Committee. These presentations should provide an understanding of the newest basic and clinical research in this field.

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