Normal "high" thyroid stimulating hormone (TSH) levels and pregnancy rates in patients undergoing IVF with donor eggs

L.H. Sordia-Hernandez[1], A. Morales Martinez[1], J.M. Gris[2], J. Herrero[2], C. Hernandez Uzcanga[1], M. Merino[1], O. Valdes[1], G. Guerrero Gonzalez[1]

[1] University Center of Reproductive Medicine, Hospital Universitario of the Universidad Autonoma de Nuevo Leon in Monterrey, Monterrey (Mexico); [2] Servicio de Ginecología Hospital Vall d´Hebron, Universitat Autonoma de Barcelona in Barcelona (Spain)

Summary

Objective: To determine if a relationship exists between pregnancy rates obtained in patients undergoing *in vitro* fertilization (IVF) with donor eggs and levels of thyroid stimulating hormone greater than 2.5 mIU/L but still within a range considered normal. *Study design:* Retrospective comparative cohort study. With prior approval of the Ethics Committee, 233 patients undergoing IVF with donor eggs, in a two-year period, were included. Patients were grouped depending on the thyroid stimulating hormone (TSH) level. Pregnancy rates were compared. Statistical analysis was made with the Chi-square test. *Results:* Pregnancy rates, depending on the TSH level, were 56.6% in patients with TSH levels below 2.49 mU/L *vs.* 21.6%, in patients with levels above 2.5 mU/L. This difference was statistically significant ($p < 0.001$). *Conclusions:* Mild abnormalities of thyroid function may adversely affect the pregnancy rates in patients undergoing *in vitro* fertilization with donor eggs. A possible alteration in endometrial function may be associated.

Key words: Thyroid stimulating hormone; In vitro fertilization (IVF); Egg donation; Clinical pregnancy rates.

Introduction

Both clinical and subclinical hypothyroidism has been associated with an increase in menstrual disturbances [1,2] and fertility problems [3, 4]. Autoimmune thyroid disease has also been associated with increased rates of infertility [5, 6].

Subclinical hypothyroidism, also called mild thyroid failure, is a health problem with a reported prevalence between 3% and 8% in the general population. It is more common in women and with advancing age [7, 8].

Alterations in serum levels of thyroid hormones have also been described as factors that adversely affect the results of *in vitro* fertilization (IVF) programs and the course of pregnancies obtained through these techniques [9].

There is controversy regarding the upper limit of normal of thyroid stimulating hormone (TSH). Some authors suggest a TSH level of 2.5 mIU/L as the upper limit of normal; however, this suggestion is not fully accepted and there is still controversy about the clinical impact that this level may have. There are reports [10] that indicate an increased incidence of spontaneous abortions in the first trimester in patients with TSH levels above 2.5 mU/L, but still within normal range.

The aim of this study was to determine if a relationship exists between pregnancy rates obtained in patients undergoing IVF with donor eggs and levels of TSH greater than 2.5 mIU/L but still within a range considered normal (4.2 mU/L according to the normal parameters in the authors' laboratory).

Revised manuscript accepted for publication August 27, 2013

Materials and Methods

The authors carried out a retrospective comparative cohort at the Hospital Universitario of the Universidad Autonoma de Nuevo Leon in Monterrey, Mexico. With prior approval of the Ethics Committee, they reviewed the reports of patients who underwent IVF procedures at the present institution between January 2008 and December 2010. Patients were contacted by phone, e-mail or telegram to request their consent to participate in this study.

Patients aged 29 to 42 years, with primary or secondary infertility, undergoing IVF procedures with donor eggs, were included. In patients with two or more cycles, the authors included only the results of the first cycle for analysis. They reviewed the patient´s age and TSH levels before performing the procedure.

Depending on TSH levels, two groups were formed, the first (group one), included patients with TSH levels of 2.49 mU/l or less; the second (group two), included patients with TSH levels between 2.5 and 4.2 mU/l.

All donor eggs underwent a protocol of controlled ovarian stimulation with follitropin alfa. The initial dose was 225 IU per day. The dose was later adjusted according to the response; stimulation was initiated on cycle day 3. The authors monitored cycles by determining serum estradiol and also used transvaginal ultrasound to monitor follicular growth. They used a gonadotropin-releasing hormone (GnRH) antagonist, ganirelix 0.25 mg per day when at least one follicle equal to or greater than 14 mm in diameter was found or when serum estradiol levels were equal to or greater than 500 pg/ml. Human chorionic gonadotropin (hCG) 10,000 IU was administered intramuscularly when at least two follicles with a diameter equal to or greater than 17 mm were found. Recovery of oocytes was performed 34 to 36 hours after the administration of chorionic gonadotropin and embryo transfer was performed on day 2 post fertilization.

In patients receiving eggs, the endometrium was prepared for embryo transfer with leuprolide acetate, which was begun on day 21 of the cycle prior to transfer; 20 IU per day were given

until menstruation. The dose of leuprolide acetate was then reduced to 10 IU per day, a dose that was maintained until two days before embryo transfer. Likewise, the authors used estradiol valerate two mg orally for three days starting on the second day of the cycle, then four mg daily for three days followed by six mg daily for three days, finally eight mg per day until week twelve of gestation if a pregnancy was achieved, or until the day a negative pregnancy test was reported, usually at day 14 after embryo transfer. Two days before embryo transfer micronized progesterone was started at doses of 200 mg intravaginally every eight hours through week 12 of pregnancy if pregnancy was achieved or until day 14 post transfer if an immunological pregnancy test was negative.

A pregnancy immunoassay was performed at 14 days post transfer. Finally, transvaginal ultrasound was performed 21 days after the transfer date to document the presence of an intrauterine gestational sac. A new vaginal ultrasound using ultrasound was performed 28 days post-transfer to detect a fetal heartbeat.

Donor eggs were healthy university students in an age range between 21 and 25 years. All TSH levels in egg donors were below 1.92 mU/L. The authors reviewed the number of eggs retrieved, the fertilization rate, number of grade I embryos, as well as the number of embryos transferred. A maximum of three embryos were transferred at early pronuclear stage on day two after insemination.

A clinical pregnancy was defined as one with an intrauterine gestational sac with the presence of one or more fetuses with a heartbeat. The authors reviewed clinical pregnancy rates according to the levels of TSH and compared them depending on whether the hormone levels were below 2.49 mU/L or above 2.5 mU/L but still within normal limits (0.27 - 4.2 mU/L) according to the reference limits of the present laboratory. Results were analyzed using the Chi-square test and Fisher exact test, when appropriated. A p value < 0.05 was considered statistically significant.

Results

The authors included a total of 233 patients. Of these, a total of 173 patients show serum TSH levels of 2.49 mU/l or less and were included in Group 1; Group 2, were formed by 60 patients with TSH levels between 2.5 mU/l and 4.2 mU/l. The mean age of patients in Group 1 was 35.1 years (SD ± 4.3 range 30 to 42), whereas the mean age in Group 2 was 36.2 years (SD ± 4.7 range 29 to 42) with no statistically significant difference ($p < 0.09$).

Regarding type of infertility, in Group 1, the percentage of patients with primary infertility was 76.3% (132/173) while 23.7% (41/173) had a history of secondary infertility. The results in Group 2 were similar, 78.3% (47/60) had a history of primary infertility, and 21.7% (13/60) secondary infertility. The difference was not significant ($p = 0.74$)

The diagnoses that were the reason for IVF in Group 1 were: low ovarian reserve in 127 cases; poor response to conventional IVF using their own eggs, 29 cases; chromosomal abnormalities, 13 cases; and severe endometriosis, four cases.

The diagnoses that were the reason for IVF in Group 2 were: low ovarian reserve in 43 cases; poor response to conventional IVF using their own eggs, ten cases; chromosomal abnormalities, four cases; and severe endometriosis, two cases.

Table 1. — *Comparison of the number of oocytes retrieved, fertilization rates, embryo quality, and number of embryos transferred.*

	Group 1	Group 2	p
Age	35.1 (SD ± 4.3, range 30 - 42)	36.2 (SD ± 4.7, range 29 - 42)	0.09
Primary infertility	76.3 % (132/173)	78.3% (47/60)	0.74
Secondary infertility	23.7% (41/173)	21.7% (13/60)	0.74
Oocytes recovered	6.21 (SD ± 2.82, range 1 – 9)	6.89 (SD ± 3.02, range 1 – 12)	0.11
Fertilization (%)	79.6	82.3	0.71
Grade 1 embryos	5.84 (SD ± 1.93, range 1 – 8)	6.27 (SD ± 2.21, range 1 – 10)	0.15
Transferred embryos	1.13	1.17	0.87

Table 2. — *Pregnancy rates and TSH levels.*

	Group 1 TSH <2.49 mU/L	Group 2 TSH 2.5–4.2 mU/L	p
Clinical pregnancy	56.6% (98/173)	21.6% (13/60)	<0.001

The mean number of oocytes retrieved was 6.21 (SD ± 2.82, range 1 - 9) in Group 1 and 6.82 (SD ± 3.02, range 1 - 12) in Group 2. The fertilization rate was 79.6% in Group 1 and 82.3% in Group 2. The number of grade 1 embryos was 5.84 (SD ± 1.93, range 1 - 8) in Group 1 and 6.27 (SD ± 2.21, range 1 - 10) in Group 2. Regarding the number of embryos transferred, the authors found an average of 1.13 embryos per cycle in Group 1 and an average of 1.17 in Group 2; the range in both groups was between 1 and 3. The difference was not significant (Table 1).

Overall clinical pregnancy rate was 47.6% (111/233). Regarding clinical pregnancy rates depending on the level of TSH, Group 1 had 173 patients with TSH levels of 2.49 or less and of these 98 became pregnant representing 56.6%. In contrast the authors found a total of 60 patients with TSH levels between 2.5 and 4.2 mU/L; of these patients 13 became pregnant representing a clinical pregnancy rate of 21.6%. This difference was statistically significant ($p < 0.001$) (Table 2).

Discussion

Alterations in thyroid function have been widely associated with anovulation, menstrual irregularities, infertility, poor outcomes in assisted reproduction programs, as well as an increased frequency of abortions [1, 11 ,4, 12]. These adverse outcomes have been demonstrated both in patients with overt hypothyroidism, as well as in patients with subclinical hypothyroidism [11].

The relationship between thyroid stimulating hormone levels and infertility has been previously reported. Two

studies report this association in patients with TSH levels within the normal range. Poppe *et al.* in 2002 [5] found higher mean TSH levels (1.30 mU/L vs. 1.10 mU/L) in infertile patients when compared with a control group of fertile women with a statistically significant difference [5]. Also, in 2004, Raber *et al.* [13] reported, when assessing the results of thyroid hormone treatment in patients with subclinical hypothyroidism, that the number of pregnancies was less if the levels of TSH were higher than 2.5 mU/L. Therefore it can be stated that even subtle alterations in TSH levels may be related to infertility.

With regards to TSH levels and pregnancy, the Endocrine Society [14] in its 2007 guidelines on the management of hypothyroidism during pregnancy and the postpartum period, recommends keeping TSH levels below 2.5 mU/L before the beginning and during pregnancy in patients diagnosed with hypothyroidism and who are undergoing treatment with thyroid hormone. It also recommends that in those patients who are diagnosed with hypothyroidism during pregnancy, treatment with thyroid hormone should be given until TSH levels below 2.5 mU/L are reached, mainly during the first trimester of pregnancy. One thing to consider is that the requirements of thyroid hormone during pregnancy increase from 30% to 50% during the first four to six weeks [14].

The results of this study showed a decrease in the number of clinical pregnancies obtained in patients undergoing IVF with donor eggs procedures with TSH levels within the normal range, but higher than 2.5 mU/L.

The effect of age on endometrial receptivity is a phenomenon previously reported [15]. In this study, the authors found that the number of pregnancies was lower in Group 2, which had an average age slightly higher than that of the patients in Group 1, but this difference in age was not statistically different. Therefore, and considering that in the present study the authors found no differences between the groups with regards to the number of oocytes recovered, the fertilization rate, and embryo quality, the authors can suggest that there may be an alteration of endometrial function associated with TSH levels above 2.5 mU/L, which could be independent of the impact of age in endometrial receptivity and very probably independent of the effect that thyroid function may have on the mechanisms of ovulation.

It is very important that the interaction of thyroid hormones and the endometrium be considered. On the one hand, endometrial receptors for both T4 and TSH among other hormones, have been described, likewise, the possibility that endometrial cells act as a producer site of thyroid hormones has recently been reported [16]. Thus, endometrium may play an important role in the genesis of abnormal reproductive function associated with thyroid function. Perhaps another explanation for the difference found in this study regarding the number of pregnancies may be related with a subtle alteration of the mechanisms of endometrial receptivity associated with thyroid hormone activity, which could be associated with mild elevations of TSH.

In this study the authors did not evaluate antithyroid antibodies. They evaluated anti-thyroid antibodies only when hypothyroidism, either clinical or subclinical, was diagnosed. The true role of antithyroid antibodies over clinical pregnancy rates in patients who underwent IVF with TSH levels in normal range should be clarified.

Conclusions

In conclusion, the authors found a decrease in the number of clinical pregnancies in patients undergoing IVF with donor eggs, with normal TSH levels, but higher than 2.5 mU/L. This may be related to a possible alteration in endometrial function; however, further studies involving a greater number of participants are needed to confirm these findings.

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Address reprint requests to:
L.H. SORDIA HERNANDEZ M.D., Ph.D.
Centro Universitario de Medicina Reproductiva,
Hospital Universitario Universidad Autonoma de Nuevo Leon
Ave. Madero y Gonzalitos s/n
Colonia Mitras Centro,
Monterrey, Nuevo León, 64460 (Mexico)
e-mail: luissordia@telmexmail.com