Original Research Paper

Volume - 11 | Issue - 02 | February - 2021 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Gynaecology

IVF OUTCOME IN FEMALES WITH HYPOTHYROIDISM WITH STRICT CONTROL OF TSH LEVELS

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ABSTRACT

OBJECTIVE- To assess the IVF outcome in infertile females with hypothyroidism after the strict control of TSH levels.

METHODS- From 1st july 2018 till 31st December 2018, total 100 infertile females were assessed. Out of 100 females, 50 females were euthyroid (Group A) and 50 females were with hypothyroidism (Group B). In group B, TSH levels were more than 4 mIU/L in initial infertility work up. Levothyroxine 25 to 50 mcg was started and dose titration was done according to the levels that were repeated after 7 to 14 days. In all these cases, embryo transfer was planned when TSH levels were less than 3 mIU/L.

RESULT- There was no difference between the two groups regarding demographic variables, number of embryos transferred and embryo quality. The pregnancy rate was 68% in the group A that was similar to 60% in the group B (P value 0.3).

CONCLUSION- Hypothyroidism contributes to increased risk of infertility and results in IVF failure. This study document that strict control of TSH levels during IVF treatment with levothyroxine results in better pregnancy rate.

KEYWORDS :

INTRODUCTION

Thyroid hormones directly affect reproductive hormones. Hypothyroidism and hyperthyroidism are common, important and often reversible or preventable cause on infertility. Euthyroid reference values for TSH assay is 0.4–4.0 mIU/L, the free T_4 assay has a range of 0.3–6.0 ng/dL and total T_4 assay range is 1.00–24 µg/mL. Subclinical hypothyroidism is a milder form of hypothyroidism defined as an elevated TSH concentration in conjunction with normal free thyroxine (FT4) levels which is 4% to 8% common among women of reproductive age (1,2). Hypothyroidism is associated with decreased plasma concentrations of estrogens and androgens with deficient LH secretion. There may be reduced libido and anovulation. So, tight control of thyroid function is must for better reproductive outcomes. As per ASRM guidelines, in hypothyroidism, TSH should be less than 2.5 µIU/ml. The thyroid autoimmunity is associated with miscarriage and fair evidence that it is associated with infertility. Levothyroxine is the recommended treatment to improve pregnancy outcomes in women with hypothyroidism and positive thyroid antibodies, especially if the TSH level is over 2.5 mIU/L (3,4). Hypothyroidism contributes to increased risk of infertility and results in IVF failure. This study document that strict control of TSH levels during IVF treatment with levothyroxine (LT4) results in better pregnancy rate.

MATERIALS AND METHODS:

The retrospective study was conducted at Advanced fertility and gynaecology center, New Delhi on patients with primary infertility between the age group of 23 to 30 years. From 1st july 2018 till 31st December 2018, total 100 infertile females were assessed. Out of 100 females, 50 females were euthyroid with TSH levels less than 4 mIU/L (Group A) and 50 females were with hypothyroidism with TSH levels more than 4 mIU/L (Group B) in initial infertility work up. Levothyroxine 25 to 50 mcg was started and dose titration was done according to the levels that were repeated after 7 to 14 days. Before starting the ovarian stimulation and on the day of HCG administration, TSH levels were done and in all these cases, embryo transfer was performed when TSH levels were less than 3 mIU/L.

Protocol

Ovarian stimulation was started on day 2 with gonadotropins, recombinant human FSH (rhFSH, Folisuge; Intas Pharmaceuticals Ltd, India or highly purified menotrophin HMG (hpHMG, Menotas; Intas Pharmaceuticals Ltd, India) in the dose of 225 to 450 IU, depending on patient profile (age, BMI, AMH, AFC) till day 6 of period followed by transvaginal follicular monitoring and dose was adjusted according to ovarian response. When follicles reached 13 to 14 mm, daily subcutaneous injection of GnRH antagonist, 0.25 mg Cetrorelix (Cetrotide, Merck Serono S.p.A, Italy), was added. When follicles reached 18 mm, 10,000 IU HCG (hpHCG, Intas Pharmaceuticals Ltd, India) was given to trigger ovulation. Transvaginal oocyte aspiration was performed before 36 h, under ultrasound guidance, using Cooks OPU needle and Cooks gamete buffer media. Embryos were further cultured in Cooks fertilization & cleavage media. Embryo transfer was done on Day 3 under transabdominal USG guidance (with full bladder). Luteal phase support was given for 14 days.

RESULT

A total of 100 females complaining of primary infertility were retrospectively included in the study. The age of the female partners was 23 to 30 years. There was no difference between the two groups regarding demographic variables, number of embryos transferred and embryo quality (Table 1). The pregnancy rate was calculated using chi square statistical analysis.

The pregnancy was positive in 34 females in euthyroid group group and in 30 females in hypothyroid group (Table 2). The pregnancy rate was 68% in the group A that was similar to 60% in the group B (P value 0.3).

Table 1 Demographic Data

Parameters	Group A (Euthyroid)	Group B (Hypothyroid)
Age		
23 - 30 years	50	50
Education		
Under Graduate	22	24
Post Graduate	28	26
Occupation		
Non working	19	22
Working	31	28
Duration of Infertility		
< 5 years	25	24
> 5 years	25	26
BMI (kg/m2)		
< 25	24	22
>25	26	28

Table 2 Outcome

Outcome	Group A (Euthyroid)	Group B (Hypothyroid)
Positive	34	30
Negative	16	20

DISCUSSION

Thyroid hormones play an important role in human reproduction both through direct effects on the ovaries and indirectly by interacting with sex hormone binding proteins. Thyroid dysfunction can lead to (reversible) menstrual irregularities and infertility (5). The rates of metabolic clearance of both androstenedione and estrone are

decreased with increased peripheral aromatization. The plasma binding activity of SHBG is decreased and the plasma concentrations of both total testosterone and estradiol are decreased and their unbound fraction increased. Hypothyroidism may also lead to a blunted LH response thereby stimulating TRH secretion and increasing serum prolactin levels. As prolactin impairs pulsatile secretion of gonadotrophin-releasing hormone (GnRH) this can lead to ovulatory dysfunction, including insufficiency of the corpus luteum with low progesterone secretion in the luteal phase of the cycle (6). This may affects the implantation of embryo and may cause IVF failure. Gracia CR et al demonstrated that controlled ovarian hyperstimulation (COH) leads to considerable perturbations in thyroid parameters, particularly in participants with preexisting hypothyroidism. They hypothesized that supraphysiologic estrogen levels associated with COH stress the hypothalamic-pituitary-thyroid axis, altering thyroid homeostasis. After rapid increases in estrogen levels, which peaks at hCG administration, TSH increases, peaking one week later, before declining to near baseline levels. This increase in TSH occurs simultaneously with significant increases in free and total T_4 (7). So TSH should be strictly monitoring in these women during IVF cycles and, if necessary, promptly adjusting the levothyroxine dose (8). Maraka S et al stated that levothyroxine treatment has been associated with better reproductive outcomes in women undergoing artificial reproductive techniques and decreased risk for pregnancy loss and preterm delivery when TSH is >4.0 mIU/L. However, well-conducted, large randomized trials with LT4 intervention at an early stage of pregnancy or preconception are still needed in this field to refine the available information (9). But, Scoccia B et al found that treated hypothyroidism is associated with significantly decreased implantation, clinical pregnancy, and live birth rates compared to euthyroid women which may be related to changes in thyroid hormone levels during COH that may exert a detrimental influence on the oocyte and/or the endometrium. A larger prospective study is necessary to assess confounding variables, confirm these findings, and determine the optimal level of TSH prior to and during COH for IVF (10). Unuane D and Velkeniers B found association of adverse fertility outcomes at TSH levels above 4.0 mIU/L. But there is little evidence to advise levothyroxine treatment at TSH levels between 2.5 and 4.0 mIU/L and more randomised controlled studies are needed to assess the pregnancy rates in subclinical hypothyroidism (11).A retrospective analysis of one thousand five hundred ninety-nine euploid blastocyst transfer cycles was done that showed the variations of TSH within the recommended range for pregnancy (≤2.5 mIU/L) have no effect on outcomes after euploid blastocyst transfer. The recommended TSH range for pregnancy (≤2.5 mIU/L) may be applied to infertile patients attempting for natural conception without a need for further adjustment (3).

CONCLUSION

Hypothyroidism contributes to increased risk of infertility and results in IVF failure. Controlled ovarian hyperstimulation also affects the TSH levels. So, the strict control of TSH levels with proper monitoring during IVF treatment with levothyroxine results in better pregnancy rate.

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