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ASSISTED REPRODUCTION TECHNOLOGIES

Donor TSH level is associated with clinical pregnancy among oocyte donation cycles

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Abstract
Purpose The purpose of the study is to evaluate the association between donor TSH level (independent of recipient TSH level) and recipient pregnancy outcome among fresh donor oocyte IVF cycles.
Methods This is a retrospective cohort study investigating 232 consecutive fresh donor-recipient cycles (200 total oocyte donors) at an academic medical center. Main outcome measures include clinical pregnancy and live birth.
Results Cycles were categorized into two groups based on donor TSH level (< 2.5 and ≥ 2.5 mIU/L). After controlling for multiple donor and recipient characteristics, the probability of clinical pregnancy was significantly lower among donors with TSH levels ≥2.5 mIU/L compared to those with TSH values <2.5 mIU/L (43.1 %, 95 % CI 28.5–58.9, versus 66.7 %, 95 % CI 58.6–73.9, respectively, $p = 0.01$). The difference in live birth rates between the two groups did not achieve statistical significance (43.1 %, 95 % CI 28.8–58.6, versus 58.0 %, 95 % CI 50.0–65.6, respectively, $p = 0.09$).
Conclusions Donor TSH level, independent of recipient TSH level, is associated with recipient clinical pregnancy. These findings suggest that thyroid function may impact the likelihood of pregnancy at the level of the oocyte.

Keywords Thyroid-stimulating hormone · Oocyte donation · Infertility · In vitro fertilization

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Capsule These findings suggest that thyroid function may impact the likelihood of pregnancy at the level of the oocyte.

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Introduction

The pivotal role which thyroid function plays in several aspects of female reproduction has been well documented by several investigators [1–3]. Given its relevance to reproduction and pregnancy, women with infertility are routinely screened for thyroid function with serum thyroid-stimulating hormone (TSH) prior to elective fertility treatment [4]. Since there is evidence that ovarian stimulation may impact thyroid function [5], timely recognition of thyroid disease prior to initiating fertility treatment may be essential to optimizing outcomes.

Several in vitro studies have correlated thyroid function to ovarian as well as endometrial physiology. Thyroid hormone may impact folliculogenesis [6, 7], ovarian steroidogenesis [8, 9], as well as endometrial receptivity [3]. However, outcome-based clinical research often cannot distinguish where along the reproductive axis (e.g., oocyte, endometrium, combination of both) thyroid hormones may have a biologic effect. The investigation of thyroid function in donor oocyte in vitro fertilization (IVF) cycles allows for independent determination of an association between thyroid function and reproductive factors occurring pre-implantation versus peri- and post-implantation. Moreover, little is known about thyroid screening among oocyte donors and whether donor TSH levels are associated with recipient pregnancy success. To this end, the objective of our study was to evaluate the association between donor TSH level (independent of recipient TSH level) and recipient pregnancy outcome among donor oocyte IVF cycles.

Materials and methods

Study population

Records from 247 consecutive fresh donor oocyte cycles completed from January 1, 2007 to December 31, 2013 at the Massachusetts General Hospital Fertility Center were reviewed. Cycles which did not have TSH values documented in the medical record, cycles canceled prior to stimulation start or hCG trigger, and cycles in which all embryos were cryopreserved were excluded from this study. A total of 232 cycles were included in the analysis. This study was approved by the Partners Healthcare Institutional Review Board.

Stimulation protocols

Oocyte donor

The majority of donors (96 % of cycles) underwent pituitary downregulation with a long luteal GnRH agonist protocol using daily subcutaneous leuprolide acetate (Lupron™, Bayer Healthcare USA) as previously described [10]. A GnRH agonist flare stimulation protocol or a GnRH antagonist (Cetrotide™, Merck Serono, U.S.A) suppression protocol was utilized in 3 % of cycles. Unless contraindicated, donors underwent pre-treatment with monophasic oral contraceptive pills (ethinyl estradiol 30 mcg, desogestrel 0.15 mg). Recombinant follicle-stimulating hormone (FSH: Gonal F™ [follitropin alpha, EMD Serono, U.S.A.] or Follistim™ [follitropin beta, Merck & Co. USA]) as well as human menopausal gonadotropin (hMG: Menopur™, Ferring, Switzerland) were prescribed and taken simultaneously in all cycles. Total gonadotropin dose was based on donor ovarian reserve markers, to a maximum of 450 IU daily. All donors were triggered with hCG (human urinary purified hCG [5000–10,000 IU]: Pregnyl™, Novarel™, or Profasi™ Merck/Schering-Plough, USA, or Ovidrel™ EMD Serono, USA). Criteria for trigger included estradiol (E_2) ≥ 600 pg/ml and ≥ 3 follicles measuring ≥16 mm. Transvaginal ultrasound-guided oocyte retrieval was performed 35 h after hCG trigger.

Recipients

All recipients underwent programmed hormone replacement after pre-treatment with monophasic oral contraceptive pills. Pituitary downregulation was achieved with daily leuprolide acetate (Lupron™ 0.5 mg, Bayer Healthcare USA) and discontinued on the day of donor oocyte retrieval. Transdermal estradiol (Vivelle-Dot™; Novartis Pharmaceuticals) was utilized for 2–3 weeks (0.2 mg patches, 1–4 patches every other day) for endometrial preparation. Both intramuscular micronized progesterone (Progesterone in Sesame Oil; Watson Pharmaceuticals Inc, Parsippany, NJ; 50 mg daily) as well as vaginal micronized progesterone (Endometrin™; Ferring Pharmaceuticals, Tarrytown, NY; 100 mg twice daily) were prescribed and initiated on the day of donor oocyte retrieval. Progesterone was continued until 13 weeks of pregnancy or negative pregnancy test. Criteria for proceeding with fresh donor embryo transfer included recipient endometrial lining ≥ 7 mm prior to initiation of progesterone. Ultrasound-guided trans-cervical embryo transfer was performed on days 2, 3, or 5 of embryo development.

Covariates and outcome measures

Oocyte donors in this practice are routinely screened with a serum TSH level prior to initiating an IVF cycle. For those donors undergoing more than one cycle at this institution, levels are updated annually. Donor TSH values closest to, but preceding a particular cycle were used for this analysis. Recipient TSH values were also tested and updated yearly. Donors or recipients with TSH values ≥ 2.5 mIU/L but < 5 mIU/L were *not* routinely treated with thyroid hormone replacement.

Covariates considered in multivariate models included donor age, recipient age, presence of male factor infertility, recipient TSH value, donor BMI, recipient BMI, donor antral follicle count, and donor status (known versus anonymous).

Primary outcomes were biochemical pregnancy (serum β-hCG level ≥ 6 mIU/mL), implantation rate (defined as the number of gestational sacs present per number of embryos transferred), clinical pregnancy per retrieval (defined as the presence of at least one gestational sac on ultrasound at 5.5–6 weeks gestation), and live birth per retrieval (defined as the birth of a viable infant at or after 24 weeks of gestation). Cycle characteristics were considered as secondary outcomes and included total gonadotropin dose received, peak estradiol (E_2) level, day of hCG trigger, recipient lining thickness (mm) and pattern (% of patients with trilaminar endometrium), number of oocytes retrieved, percent metaphase II (M2) mature oocytes retrieved, fertilization rate (number of two pronuclear zygotes [2PN] visualized 1 day following oocyte retrieval/number of retrieved oocytes × 100), day of embryo transfer, and cycle cancelation prior to transfer.

Statistical analysis

A level of 2.5 mIU/L was utilized to dichotomize women into high or normal TSH groups. Donors with a pre-IVF cycle TSH value ≥ 2.5 mIU/L were grouped together. This clinically relevant level was utilized given recent guidelines recommending that correction of pre-conceptional TSH to < 2.5 mIU/L should be considered, even among euthyroid women [11].

Univariate analyses were performed on data obtained from each donor's first cycle at our institution. Chi-square and

Fishers' exact tests were applied as indicated for categorical variables. *P* trend values were calculated from linear regression analysis of continuous variables and Poisson regression analysis of ordinal variables (number of previous cycles and donor parity). Multivariate analyses were performed on data from all available cycles. The associations between TSH category and clinical outcomes were evaluated using generalized linear mixed models with random intercepts to account for within-person correlations in repeated cycles while adjusting for potential confounders. Linear mixed models were used when outcomes were continuous (e.g., peak estradiol, recipient lining thickness, total gonadotropin dose) and mixed Poisson models were utilized for ordinal outcomes (e.g., day of HCG trigger, number of oocytes retrieved, number of embryos transferred). Mixed logistic models were built to evaluate all other rates and primary pregnancy outcomes. Results of multivariate modeling are presented as adjusted means or probabilities adjusted for confounders. A P value < 0.05 was considered statistically significant. All statistical analyses were performed using SAS v9.3 (SAS Institute, Cary, NC).

Results

Two hundred thirty-two consecutive fresh donor-recipient cycles (200 total oocyte donors) were included in this analysis. Mean donor age (standard deviation) at first cycle was 27.1(3.8) years. Overall clinical pregnancy and live birth rates for this cohort were 61 and 55 %, respectively. Sixteen spontaneous abortions (SABs) occurred prior to 12-week estimated gestation in this cohort of women and were exclusive to the group with donor TSH level < 2.5 mIU/L. Twenty-one percent (49 cycles) of cycles occurred among donors with TSH levels ≥ 2.5 mIU/L, and 29 % (68 cycles) of cycles occurred among recipients with TSH levels ≥ 2.5 mIU/L.

Demographic and clinical characteristics of donors and their recipients at the time of the donor's first cycle at Massachusetts General Hospital Fertility Center are listed in Table 1. Results are presented by donor TSH level (<2.5 mIU/L or ≥ 2.5 mIU/L). There were no statistically significant associations between donor TSH group and any demographic or clinical characteristics, other than donor parity. Donor TSH level < 2.5 mIU/L was associated with higher donor parity. The majority of donors were nulliparous at the time of last cycle (n = 135).

When all cycles were analyzed, cycle characteristics were not associated with donor TSH in age-adjusted models (Table 2). Cycle outcome, however, was related to donor TSH (Table 3). Lower rates of biochemical pregnancy, implantation, clinical pregnancy, and live birth, respectively, were observed among cycles with high donor TSH levels. In age-adjusted models, cycles with donor TSH levels ≥ 2.5 mIU/L had a significantly lower probability of biochemical and clinical pregnancy and lower implantation rate. Adjusting for potential confounders such as male factor infertility, donor age, recipient age, recipient TSH level, donor BMI, recipient BMI, donor antral follicle count, and donor status (known versus anonymous) did not appreciably alter the results. Recipient TSH level was not related to clinical outcome in these multivariate models (data not shown).

In order to test for heterogeneity in the relationship of TSH and outcome by insemination type (ICSI versus conventional) and donor status (known versus anonymous), interaction terms were placed into multivariate models. The relationship between TSH and clinical pregnancy did not vary by insemination type or by donor status (data not shown).

Since donor parity is higher among donors with TSH < 2.5 mIU/L, additional analyses adjusting for donor parity were performed by including it as a covariate in multivariate models for the outcomes of clinical pregnancy and live birth. Controlling for donor parity did not significantly change the relationship between donor TSH and clinical pregnancy (P = 0.02) or donor TSH and live birth (P = 0.13).

Finally, we performed a sensitivity analysis by excluding donors with TSH levels ≥ 5.0 mIU/L and reanalyzing clinical pregnancy. There were 4 cycles among donors with TSH levels ≥ 5.0 mIU/L. After exclusion, the magnitude and direction of the relationship between clinical pregnancy and TSH did not meaningfully change (for TSH ≥ 2.5 mIU/L and clinical pregnancy prior to exclusion: multivariate odds ratio 0.4, 95 % CI 0.2–0.8, p = 0.01; for TSH ≥ 2.5 mIU/L and clinical pregnancy after exclusion: multivariate odds ratio 0.4, 95 % CI 0.2–0.8, p = 0.02).

Discussion

Among a cohort of women undergoing oocyte donation cycles, pre-treatment donor TSH levels ≥ 2.5 mIU/L were associated with lower recipient implantation and clinical pregnancy rates compared to donor TSH levels < 2.5 mIU/L. To our knowledge, this is the first study evaluating the relation of donor thyroid function with recipient pregnancy outcome.

The finding that donor TSH level, independent of recipient TSH level, was associated with recipient clinical pregnancy implies that thyroid function may impact the likelihood of pregnancy prior to fertilization and implantation. Although there are data implicating thyroid hormones as key mediators in folliculogenesis and endometrial receptivity [2, 3, 12, 13], clinical studies that do not utilize a donor model largely cannot differentiate between the potential impacts on donor versus host when evaluating overall pregnancy outcomes.

Although the live birth rate was lower among patients with donor TSH levels ≥ 2.5 mIU/L, this difference did not achieve statistical significance, possibly due to the fact that this analysis was underpowered (1-β = 0.47). Nonetheless, larger

Table 1 Characteristics of donor and recipient at donor's first cycle, by donor TSH, mean (SD), or percent (frequency)

	TSH 0.4–2.4 mIU/L	TSH 2.5–9.0 mIU/L	*P* value
n	161	39	
Donor TSH (mIU/L)	1.4(0.5)	3.8(1.4)	<0.01
Donor age (years)	27.2(3.7)	26.5(4.0)	0.27
Recipient age (years)	41.0(4.7)	42.2(5.0)	0.14
Donor BMI (kg/m^2)	23.4(3.1)	23.4(3.4)	1.00
Recipient BMI (mg/m^2)	24.2(4.4)	24.0(4.1)	0.72
Recipient TSH (mIU/L)	2.1(1.0)	2.2(1.1)	0.70
Donor AFC	19.2(6.9)	19.4(7.7)	0.86
Donor D3 FSH (IU/L)	6.1(1.6)	6.3(1.7)	0.65
Total number of previous cycles[a]	1.3(1.4)	1.2(1.3)	0.67
Known donor, %(*n*)	16.2 %(26)	15.4 %(6)	0.91
Male factor, %(*n*)	16.8 %(27)	7.7 %(3)	0.15
Uterine factor, %(*n*)	2.5 %(4)	0.0 %(0)	1.00
ICSI, %(*n*)	43.5 %(70)	35.9 %(14)	0.39
Donor parity[a]	0.60(0.90)	0.26(0.76)	<0.01

TSH thyroid stimulating hormone, *BMI* body mass index, *AFC* antral follicle count, *FSH* follicle stimulating hormone, *ICSI* intracytoplasmic sperm injection

[a] Based on donor's last cycle at this institution

studies are needed to assess whether the association between donor TSH and clinical pregnancy will translate into an impact on recipient live birth. Interestingly, all SABs occurred to recipients with donor TSH levels < 2.5 mIU/L. Given the small number of SABs, it is not possible to draw any conclusions regarding a possible association with donor TSH. A previous study evaluating TSH levels in ovulation induction cycles did demonstrate a higher rate of SABs among women with pre-treatment TSH levels <2.5mIU/L [14].

In addition to the well-documented effects of thyroid disease on ovulation [13, 15], there is evidence to suggest that thyroid function is associated with pregnancy outcome even in

Table 2 Cycle characteristics by donor TSH, adjusted mean, or adjusted probability (95 % CI)

	TSH 0.4–2.4 mIU/L	TSH 2.5–9.0 mIU/L	*P* value
Number of cycles	183	49	
Total gonadotropin dose (IU), mean	1946(1809–2084)	1842(1610–2074)	0.42
Peak E_2 (pg/mL), mean	2553(2378–2728)	2645(2370–2920)	0.56
Day of hCG, mean	12.1(11.5–12.6)	12.2(11.2–13.3)	0.87
Recipient lining on day of trigger (mm), mean	9.9(9.6–10.2)	10.4(9.5–11.2)	0.33
Recipient multilayered lining, %	94.9 %(90.0–97.5)	93.6 %(80.2–98.1)	0.74
Number of eggs retrieved, mean	14.1(13.2–15.2)	14.3(12.5–16.3)	0.88
Intracytoplasmic sperm injection (ICSI), %	43.2 %(35.9–50.8)	32.7 %(20.7–47.5)	0.20
Percent mature oocytes (M2), %	85.7 %(83.4–87.7)	84.7 %(79.9–88.5)	0.67
Fertilization rate (#2PN/# retrieved oocytes), %	73.3 %(70.4–76.0)	72.5 %(66.7–77.6)	0.78
Cleavage rate, %	99.0 %(98.2–99.4)	99.3 %(97.6–99.8)	0.54
Number of embryos transferred, mean	1.7(1.5–1.9)	1.7(1.4–2.2)	0.70
Day 5 transfer (versus day 2 or 3), %	59.8 %(51.5–67.6)	54.8 %(38.8–69.9)	0.57
Cancellation prior to transfer, %	3.8 %(1.8–8.0)	4.1 %(1.0–15.7)	0.93

Results are adjusted for donor age, except for recipient lining and pattern which are adjusted for recipient age

E_2 estradiol, *hCG* human chorionic gonadotropin, *2PN* two pronuclear embryo observed on the day following in vitro fertilization (i.e., normal fertilization)

Table 3 Cycle outcome by donor TSH, crude and adjusted rate (95 % CI)

	Crude rates (frequency)		Age-adjusted			Multivariate-adjusted		
	TSH 0.4–2.4 mIU/L	TSH 2.5–9.0 mIU/L	TSH 0.4–2.4 mIU/L	TSH 2.5–9.0 mIU/L	*P* value	TSH 0.4–2.4 mIU/L	TSH 2.5–9.0 mIU/L	*P* value
Number of cycles	183	49	183	49		183	49	
Biochemical pregnancy	72.7 % (133)	55.1 % (27)	72.7 % (65.4–78.9)	55.6 % (40.9–69.4)	0.03	73.9 % (66.2–80.3)	56.0 % (40.3–70.6)	0.03
Implantation rate	54.8 %	34.1 %	53.0 % (45.6–60.2)	34.4 % (22.8–48.1)	0.02	53.2 % (45.3–60.8)	34.1 % (21.9–48.7)	0.03
Clinical pregnancy	66.1 % (121)	42.9 % (21)	66.1 % (58.5–73.0)	43.0 % (29.2–58.0)	<0.01	66.7 % (58.6–73.9)	43.1 % (28.5–58.9)	0.01
Live birth	57.9 % (106)	42.9 % (21)	57.9 % (50.3–65.2)	42.9 % (29.3–57.6)	0.07	58.0 % (50.0–65.6)	43.1 % (28.8–58.6)	0.09

Adjusted for male factor, donor age, recipient age, recipient TSH, donor BMI, recipient BMI, donor AFC, and donor status (known versus anonymous)

the setting of superovulation and IVF. Despite treatment, women with hypothyroidism may have lower chances of pregnancy success after IVF [16]. Subclinical hypothyroidism may impact reproduction as well, and treatment in women with elevated TSH but normal free thyroxine levels has been shown to improve IVF outcome [17]. Our results are in line with previous findings suggesting that TSH and thyroid function are associated with IVF success.

Although an exact mechanism cannot be assumed, our results imply that thyroid function may contribute to outcomes prior to implantation, possibly at the level of the oocyte. Similarly, a study by Cramer et al. (2003) also highlighted the importance of pre-implantation thyroid function by demonstrating that elevated TSH correlated with poor fertilization in IVF but not with overall success rate [18]. Moreover, thyroid hormones have been found in follicular fluid [19] and their receptors are present on granulosa cells [8], further lending plausibility to the notion that thyroid dysfunction may impact ovarian and follicular physiology and oocyte quality. Of note, we did not find any difference in fertilization rate among donors with high or low TSH levels, nor did we observe any heterogeneity in the relationship of donor TSH and clinical pregnancy by insemination type (conventional insemination versus ICSI [intracytoplasmic sperm injection]). Despite the negative association between donor TSH and clinical pregnancy, we did not observe any associations with cycle characteristics that could account for the relationship.

Interestingly, recipient TSH was not associated with clinical outcomes in our multivariate models. This finding suggests that among women undergoing oocyte donation cycles, TSH level prior to in vitro fertilization may be more critical for implantation and clinical pregnancy than post-embryo transfer TSH level. It is important to note, however, that at our institution, recipients with an elevated TSH level ≥ 5.0 mIU/L or known thyroid disease do not usually undergo an IVF cycle until treatment has been initiated. Therefore, our study is not able to discern the impact of untreated thyroid disease on IVF outcome.

We utilized a TSH level of 2.5 mIU/L as our cut point for the categorization of donors into high and normal TSH groups. This level was chosen due to evidence that pregnancy reference intervals for TSH are lower than those of the general population [20], and recent guidelines suggest that pre-conceptional TSH should be corrected to <2.5 mIU/L, even in euthyroid women [11]. This statement is not without controversy, as some studies have not observed a relationship between pre-conceptional TSH level and fertility treatment outcome among euthyroid women [14, 21, 22]. Nevertheless, our current results suggest that pre-fertilization donor TSH level may play a role in treatment outcome, specifically among women undergoing IVF with donor oocytes. Excluding cycles with donor TSH levels ≥ 5.0 mIU/L did not appreciably change the relationship between donor TSH and clinical pregnancy, implying that our results were not sensitive to the inclusion of potentially inadequately treated hypothyroid donors.

The strengths of our study include its unique objective and donor/recipient design, allowing for the elucidation of pre- versus post-fertilization and implantation relations of TSH with pregnancy outcome. Since all donors and recipients are routinely screened with a TSH level and closely followed for pregnancy outcome in this center, the likelihood for selection bias based on exposure status or differential follow-up is minimal. In terms of limitations, as with most observational studies, we cannot draw conclusions about causality without further investigation. Moreover, we do not routinely check thyroid antibody status or free thyroxine on patients with TSH levels < 5.0 mIU/L; therefore, these values were not consistently available for analysis. Pre-treatment TSH levels may not fully represent thyroid function during fertility treatment, as there are data suggesting that TSH levels fluctuate during stimulated cycles [5]. Since this study focused on women undergoing assisted reproductive technology at a single institution, the results may not be generalizable to women undergoing natural conception attempts or those who conceive spontaneously.

In summary, TSH level ≥ 2.5 mIU/L in an oocyte donor may negatively impact implantation and clinical pregnancy among donor oocyte recipients. Although the traditional focus has been on ovarian reserve and donor stimulation protocol as predictors of outcome, the findings of this study provide invaluable insight into the potentially modifiable impact of thyroid function on pregnancy in a donor recipient model. Since recipient TSH was not associated with IVF outcomes, it is evident that the influence of thyroid function during the use of either donor oocytes or autologous oocytes is complex and warrants additional investigation. Future studies should further stratify patients by thyroid antibody status, as well as investigate long-term neonatal outcomes.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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