TSH Abnormalities and Fetal Loss

INTRODUCTION

The present review will examine the impact of maternal serum thyrotropin (TSH) abnormalities on fetal loss (defined as spontaneous miscarriage, intrauterine death and neonatal death). This interaction, and the potential to prevent fetal loss with appropriate intervention, is one of the core issues of the ongoing debate regarding universal screening during pregnancy for thyroid disease. Although the majority of the literature has centered on hypothyroidism, and in particular subclinical hypothyroidism, an important literature also exists on the interaction of fetal demise and hyperthyroidism. In 1969, Jones and Man published a landmark article evaluating the impact of abnormal serum butanol-extractable iodine (BEI) levels and miscarriage, premature deliveries and stillbirths. Low BEIs, consistent with hypothyroidism, was reported in 6% (60/1000) of the women evaluated. Women with low BEIs had a significant increase in miscarriages, prematurity and stillbirths compared to 1,255 women with normal BEIs during pregnancy (1). Similarly, women with elevated BEIs, consistent with hyperthyroidism, had an increase in deliveries without full-term surviving infants compared to controls (31.8% vs. 12.6% respectively).

INCIDENCE

Nine studies have evaluated the incidence of hypothyroidism during pregnancy (2-10). As demonstrated in Table 1, the studies vary in their definition of hypothyroidism, along with the time of pregnancy at which screening occurred. Two studies evaluated less than 1000 women, raising questions of the validity of their findings (5, 10). Investigations performed in the United States (excluding the study with only 209 subjects) have yielded remarkably similar results. Overall, the incidence of hypothyroidism was between 2.2% to 2.5%, with an incidence of subclinical and overt hypothyroidism ranging from 2.2% to 2.3% and 0.2% to 0.3% respectively. The overall rate of hypothyroidism in the United Kingdom was similar at 2.6%, however there was an increased incidence of overt hypothyroidism at 1.0%. Studies in Finland, the Netherlands, and India have yielded disparate results with rates of hypothyroidism of 4.8%, 0.5%, and 11.1% respectively.

Determination of the incidence of hyperthyroidism in pregnancy is complicated by the normal physiological increase in human chorionic gonadotropin (hCG) which occurs in the first half of pregnancy. Due to cross reactivity of hCG at the TSH receptor, a percentage of pregnant women will develop a transiently suppressed serum TSH. In order to grapple with this issue, studies have attempted to differentiate women with low serum TSH during pregnancy secondary to hCG stimulation, from those individuals with TSH values which are suppressed secondary to ongoing thyroid disease. As demonstrated in Table 2, (5, 6, 8, 9, 10-14), low TSH values can be found in up to 34% of all pregnancies. However, suppressed serum TSH levels, those below <0.03 μIU/ml, is found in 2% of pregnant women. The majority of these women present with subclinical, as opposed to overt, hyperthyroidism.

Finally, a small, but undefined, percentage of women who become pregnant will already be on treatment for previously diagnosed hypothyroidism or hyperthyroidism. As documented in the Colorado Thyroid Disease Prevalence Study, a statewide health fair conducted in 1995 with 25,862 participants, only 60% of individuals treated with thyroid medication (n=1525) were euthyroid at the time of screening (15). Given the well documented need to increase the dose of levothyroxine during pregnancy in the majority of women (16, 17), it is not surprising that Hallengren et al found 49% of pregnant women on levothyroxine therapy (31/63) had TSH values outside the reference range (18). In particular, 12 women had TSH values below 0.40 μIU/ml and 19 women had TSH levels which exceeded 4.0 μIU/ml. Similar results were reported in the FaSTER (First and Second Trimester Evaluation of Risk for Fetal aneuploid) trial, which evaluated first and second trimester TSH levels in 389 pregnant women with a diagnosis of hypothyroidism. Forty-three percent of women had a TSH above 2.5 μIU/ml in the first trimester and 33% of women had a TSH exceeding 3.0 μIU/ml in the second trimester (19).

FETAL LOSS-HYPOTHYROIDISM

Thirteen articles have investigated the relationship between fetal loss and hypothyroidism. The studies vary markedly in the following criteria: number of women enrolled, gestational week of enrollment; definition of thyroid dysfunction; treatment and when initiated; and retrospective vs. prospective. Studies in which information is not provided on the gestational week of initial thyroid sampling may have misleading data on the incidence of miscarriage (for example, if initial screening occurred at 16 weeks most miscarriages would have already occurred). Three retrospective clinical series are reported in the following paragraph.

In one of the earliest reports (1981), Montoro et al describe the outcome of 9 hypothyroid women during 11 pregnancies. In their study, the incidence of fetal death was 10% (n=1) (20). Davis et al reported on 28 pregnancies in 25 women who were hypothyroid during pregnancy. Sixteen women were clinically hypothyroid and 12 women presented with subclinical hypothyroidism (21). Levothyroxine intervention occurred in 26 of the pregnancies and was initiated at varying times (between 4-40 weeks gestation). Fetal death occurred in one individual with subclinical hypothyroidism (1/12 or 8%) and two women with clinical hypothyroidism (2/16 or 13%). A similar, but larger series was published by Leung et al, in which 68 women with overt (n=23) and subclinical (n=48) hypothyroidism were followed prospectively (22). One fetal death occurred in a woman (1/23=4%) who had discontinued levothyroxine therapy, resulting in a TSH of 289 μIU/ml.

Table 3 summarizes nine articles which will be described in the remainder of this section. Allan et al evaluated TSH levels and miscarriage in 9,403 women who were screened for neural tube defects and Down's syndrome (3). They reported that second

trimester miscarriages were increased four-fold in women with elevated TSH levels as compared to controls. In hypothyroid women, the greatest increase in miscarriage was seen in individuals whose TSH was ≥10.0 μIU/ml as compared to women with TSH values between 6.0 mU/L and 9.99 μIU/ml (8.1% vs. 2.9% respectively). Abalovich et al followed 150 pregnancies in 114 women who were being treated for hypothyroidism (23). The outcome of the 51 pregnancies conceived while the woman was hypothyroid was compared to the 99 pregnancies conceived in euthyroid women. Women who were adequately treated during pregnancy had a marked decrease in miscarriages as compared to women who were inadequately replaced with levothyroxine.

Casey et al reported on pregnancy outcome of 17,298 women screened for thyroid disease prior to the 20th week of pregnancy (4). No difference in the rate of fetal death between women with subclinical hypothyroidism and controls was found. They also reported no increase in fetal deaths in women with isolated hypothyroxinemia (normal TSH and decreased free T_4) (24). Similar findings were described by Matalon et al. One thousand one hundred and two deliveries, out of 139,168 deliveries, were in hypothyroid women. The perinatal death rate in the two groups was virtually identical (25).

In 2008 Cleary-Goldman et al published an analysis of pregnancy outcome and thyroid function in the 10,990 women who participated in the FaSTER trial (7). Designed to study first trimester ultrasound translucency measurements, along with first and second trimester serum markers for Down syndrome, TSH and free T_4 values were analyzed in all women. As compared to controls, neither miscarriage nor fetal death was related to thyroid function levels in either trimester.

Four studies have already been published in 2009 evaluating the relationship between thyroid dysfunction and fetal demise. Sahu et al reported an increase in intrauterine demise in women with overt hypothyroidism, but not subclinical hypothyroidism, as compared to controls (10). On the other hand, Mannisto et al reported no difference in miscarriage or perinatal mortality rates between controls and women with either subclinical or clinical hypothyroidism (8). Hallengren et al reported on pregnancy outcome in 63 women on thyroid replacement therapy. Fetal loss was significantly greater in women with abnormal thyroid function (either hypothyroidism or hyperthyroidism) as compared to women who were euthyroid on replacement (29% vs. 6%, $p < 0.05$) (18). Finally, in a prospective study, Benhadi et al evaluated the impact of increased maternal serum TSH levels with subsequent child loss, defined as a combination of miscarriage, fetal and neonatal death (this study not included in Table 3). A positive linear relationship was reported between child loss and TSH, which extended into the normal TSH range (9).

FETAL LOSS-HYPERTHYROIDISM

Few studies have investigated the association between hyperthyroidism and fetal loss. As a component of their previously described cohort, Casey et al examined the relationship between subclinical hyperthyroidism and pregnancy outcomes (13). Of the 25, 765 women screened, 433 presented with subclinical hyperthyroidism (1.7%). The rate of neonatal death between these two groups was indistinguishable (0.2% vs. 0.2%, p=ns). Similarly, Mannisto reported similar rates of miscarriage and perinatal mortality in women with hyperthyroidism (either overt or subclinical) as contrasted to controls (8). Anselmo et al evaluated the fetal impact of thyroid hormone excess by analyzing fetal outcome in mothers with thyroid hormone resistance (THR) (26). An increased miscarriage rate was seen in mothers affected by THR. This may have preferentially impacted fetuses that were unaffected by THR. Unaffected infants with THR mothers had suppressed TSH levels at birth and decreased birth weights, further demonstrating the impact of excess thyroid hormone on the developing fetus.

CONCLUSION

In conclusion, the incidence of thyroid dysfunction, defined as either hypothyroidism or hyperthyroidism during pregnancy, is approximately 5%, or one out of every 20 women. The relationship between thyroid dysfunction and fetal demise remains murky. No relationship exists in women with subclinical hyperthyroidism, and the studies in overt hyperthyroidism are mixed. The picture is even more confusing in respect to hypothyroidism. Overt hypothyroidism appears to be linked to fetal demise, but whether or not a relationship exists between fetal demise and subclinical hypothyroidism is simply unclear. Specifically, the published studies to date are evenly split between those that have, and have not, found a relationship between subclinical hypothyroidism and fetal demise. The increasing rate of fetal loss as maternal serum TSH rises through the normal range documented by Benhadi et al, challenges us to question what is considered a normal TSH. Much light will be shed on the relationship between fetal loss and thyroid dysfunction in the ensuing five years. Research is increasing at a rapid rate, and ongoing prospective studies in Cardiff, the NIH and Lecce will yield much needed clarity.

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Table 1. Nine Studies that evaluated the incidence of hypothyroidism during pregnancy

Author	Year	N	Country	Gestational Week	TSH	T_4	Hypothyroidism Subclinical	Overt
Klein et al (2)	1991	2000	USA	15-18 weeks	>6 mU/L	<2 SD	2.2%	0.3%
Allan et al (3)	2000	9403	USA	15-18 weeks	>6 mU/L	NR	2.2%	
Casey et al (4)	2005	17,298	USA	<20 weeks	>97.5th percentile	<0.680 ng/dl	2.3%	0.2%
Aoki et al (5)	2007	209	USA		>5.0 mU/L		6.9%	
Vaidya et al (6)	2007	1560	UK	Median 9th week	>4.3 μIU/ml	<12.0 pmol/l	1.6%	1.0%
Cleary-Goldman et al (7)	2008	10,990	USA	1st Trimester	>97.5th percentile	<2.5th percentile	2.2%	0.3%
Mannisto et al (8)	2009	5,805	Finland	12th week	>95th percentile	<5th percentile	3.9%	0.9%
Benhadi et al (9)	2009	2,497	Netherlands	Mean 13th week	>5.6 mU/L	<7.5 pmol/L	0.5%	
Sahu et al (10)	2009	633	India	13-26 weeks	>5.5 mU/L	NR	6.5%	4.6%

NR = Not reported; SD = standard deviation; Gestational week = the gestational week during pregnancy that the sample was obtained.

Table 2. Nine studies that evaluated the incidence of hyperthyroidism during pregnancy

Author	Year	N	Country	Gestational Week	TSH μIU/ml	T_4 pmol/L	Hyperthyroidism Subclinical	Overt
Glinoer (11)	1997	760	Belgium	8-14 weeks	<0.02 μIU/ml	>26.0		2.4%
Yeo et al (12)	2001	184	Singapore	8-14 weeks	<0.36 mU/L	>19.1	22%	12%
Casey et al (13)	2006	25,765	USA	<20 weeks	<2.5th percentile	>1.75 (ng/dl)	1.7%	0.4%
Aoki et al (5)	2007	209	USA		<0.1 μIU/ml		2.9%	
Vaidya et al (6)	2007	1560	United Kingdom	Median 9th week	<0.03 μIU/ml	>23.0	1.2%	0.7%
Lazarus & Kahelamanon (14)	2007	1497	United Kingdom	9-15 weeks	<0.02 μIU/ml	>23.1	1.3%	0.17%
Mannisto et al (8)	2009	5805	Finland	12th week	<95th percentile	>5th percentile	3.5%	1.3%
Benhadi et al (9)	2009	2,497	Netherlands	Mean 13th week	<0.34 μIU/ml	>21.1	5.0%	0%
Sahu et al (10)	2009	633	India	Mean 13th week	<0.5 mU/L	NR	0.9%	0.8%

NR = not reported; TSH = μIU/ml; FT_4 = free thyroxine (pmol/L) or ng/dl in one study as noted;
Gestational week = the gestational week during pregnancy that the sample was obtained

Table 3. **Nine studies that evaluated the relationship between hypothyroidism and fetal demise**

Author	Year	Country	Number Total	Number Hypothyroid	Thyroid		Miscarriage Hypothyroid	Miscarriage Control	Fetal Death Hypothyroid	Fetal Death Control	Weeks Gestation	P
Allan et al (3)	2000	USA	9,403	209	Hypothyroidism definition TSH 6 μIU/ml		3.8%	0.9%	NR	NR	15–18 weeks	<0.05
Abalovich et al (23)	2002	Argentina	150	35 – Subclincal 16 – Overt	Adequate Rx TSH 4 mU/L		60% – Overt 71% – Subclinical	0% – Overt 0% – Subclinical	NR	NR	NR	P< 0.006
Casey et al (4)	2005	USA	17,298	404	Subclinical Hypothyroidism TSH > 97.5th percentile T_4 < 0.680 ng/dl		NR	NR	0.5%	0.5%	<20 weeks	NS
Matalon et al (25)	2006	Israel	139,168	1,102					1.4%	1.3%		NS
Casey et al (24)	2007	USA	17,298	233	Isolated Hypothyroxenemia TSH 2.5th – 97.5th T_4 < 0.680 ng/dl		NR	NR	0%	0.5%	<20 weeks	NS
Cleary-Goldman et al (7)	2008	USA	10,990	240 – Subclinical 243 – Hypothyroid	Subclinical Hypothyroidism TSH >97.5th Normal fT_4	Hypothyroid Normal TSH FT_4 < 2.5th	0.4% – Subclinical 0.0% – Hypothyroid	0.6%	0.0% – Subclinical 0.4% – Hypothyroid	0.3%	1st Trimester	NS
Sahu et al (10)	2009	India	633	41 – Subclinical 29 – Clinical hypothyroidism	Subclinical Hypothyroidism TSH > 5.5 μIU/ml Normal FT_4	Clinical TSH > 5.5 μIU/ml Low fT_4	NR	NR	25% – Subclical 13% – Overt	1.4%	13–26 weeks	NS p=0.0004
Mannisto et al (8)	2009	Finland	5,805	224 – Subclinical 54 – Clinical	Subclinical Hypothyroidism TSH > 95th Normal fT_4	Clinical TSH > 95th fT_4 < 5th	Subcl – 16.1% Clin – 22.2%	19.5%	Subcl – 1.8% Overt – 1.9%	0.8%	12th week	NS
Hallengren et al (18)	2009	S weden	63	19 – Hypothyroidism 12 – Hyperthyroidism	Normal TSH 0.4 – 4.0 μIU/ml		NR		Euthyroid – 6% Hypothyroid or Hyperthyroid – 29%		1st Trimester	p<0.05

NR = not reported
FT_4 = Free thyroxine
Wks = weeks

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