The Role of iodine in the Thyroid Status of Mothers and Their Neonates

Rabindra Nath Das

Department of Statistics, The University of Burdwan, Burdwan, West Bengal, India

Correspondence: Dr. R.N. Das, Associate Professor, Department of Statistics, The University of Burdwan, Burdwan, W.B., India; E-mail: rabindasbwn@yahoo.co.in

Received: September 20, 2010
Accepted: October 11, 2010

Abstract. It is well known that iodine is an indispensable component of thyroid hormones. The discovery of iodine deficiency and its adverse effects upon human beings is an instructive example of the transfer of scientific and medical knowledge to the benefit of the public health. Physicians have known for more than a century that deficient iodine intake is associated with endemic goiter, cretinism, and that it increases neonatal mortality. In this paper, statistical analysis is used to objectively verify the mathematical relationships of deficient maternal urinary iodine to the results of thyroid function tests (T₃, T₄, and TSH) of both low-iodine mothers and their neonates. In general, complex functional systems, such as human physiological mechanisms, are more easily interpreted based on true mathematical models. The mathematical relationships of the multiple variables analyzed in this paper are established by the statistical method of joint generalized linear modeling. The results of the statistical analysis are highly relevant to the diagnostic and therapeutic practices of clinicians who attend to pregnant women, their in utero embryos and fetuses, the women’s neonates after delivery, and by extension, the developmental (especially neurological) well-being of the off-springs as they mature. The analysis establishes relationships important to the health and well-being of both mothers and their neonates; simultaneously, it shows the exceptional utility of the statistical method of joint generalized linear modeling.

Keywords Hyperthyroidism • Hypothyroidism • Iodine • Joint generalized linear model • Structured dispersion • Thyroid functions • Urinary iodine excretion

Introduction

Iodine is an essential component of thyroid hormones, and its importance stems mainly from that role. The most obvious consequence of iodine deficiency is goiter. This adaptive response is mediated principally by serum thyroid stimulating hormone (TSH). As the quantity of thyroid hormone reaching the pituitary thyrotrophic cells decreases, the cells are disinhibited and increase their synthesis and secretion of thyroid hormone. The increased TSH stimulates most functions of the thyroid gland. With too little iodine to synthesize enough thyroid hormone to suppress TSH secretion, the TSH remains high and stimulates hypertrophy of the thyroid gland. If the iodine deficiency is mild and the thyroid gland increases thyroid hormone production, the affected individual has no apparent consequence other than an enlarged thyroid.

In the past, when this disease entity was widespread among a particular population, it was labeled “endemic goiter.” The disease was recognized as a significant public health issue. It received much less attention, however, than other pressing health problems such as infectious diseases. Cre-
tinism is known to be associated with endemic goiter, but the existence of a continuum from mild mental retardation to gross neurological impairment has only been widely appreciated in the last several decades (see reviews by Delange et al.\cite{1,2}).

The World Health Organization (WHO) recently increased its recommended iodine intake during pregnancy from 200-to-250 μg/L. WHO also suggested that a median urinary iodine concentration of 150-to-249 μg/L indicates adequate iodine intake in pregnant women. The TSH concentrations in blood collected from newborns 3-to-4 days after birth may be a sensitive indicator of even mild iodine deficiency during late pregnancy.\cite{3,4}

The term “iodine deficiency disorders” serves to emphasize the many other consequences of iodine deficiency.\cite{5} Of these disorders, disruption of reproductive function and damage to the developing fetus and infant are the most severe. Aspects of this topic have been reviewed in detail elsewhere.\cite{6,7,8,9}

The International Council for Control of Iodine Deficiency Disorders (ICCIDD) recommends a daily intake of 100 μg iodine for nonpregnant adults.\cite{10,11,35,36} This number is based on studies of iodine accumulation and turnover, the T₄ dose required to maintain euthyroidism in athyreotics, T₄ disposal rates, and the amounts of iodine necessary to prevent goiter in populations.\cite{11,12} Pregnant women need more than this baseline requirement to cover the iodine needs of the developing fetus and to compensate for increased renal iodine losses. In 2010, the ICCIDD recommended an intake of 200 μg for pregnant and lactating women.\cite{11} Renal clearance of iodine increases during pregnancy;\cite{13} in one study, for example, the concentration of iodine in the urine of women from a mildly iodine-deficient geographic area was 60% higher during pregnancy.\cite{14}

Hypothyroxinemia, elevated serum TSH, enlargement of the thyroid gland (by 10% to 50%), and goiter are the most common measured consequences for the pregnant woman. However, these effects can be prevented by adequate iodine supplementation.\cite{12}

Iodine deficiency increases neonatal mortality. We emphasize this statement so that iodine deficiency can take its proper place among the disorders that kill children. “Child survival” is something of a buzzword in international aid circles, and showing its relation to iodine deficiency helps direct resources toward its correction.\cite{15}

So far, many authors have conducted clinical and physiological studies of the effects of iodine on pregnant women and their neonates. But it is difficult to understand the functional relationships of iodine to mothers and their neonates based solely on clinical and physiological studies. In general, complex functional systems such as human physiological mechanisms are more easily interpreted based on true mathematical models.

Our literature search shows that a paucity of reports on the effects of iodine on mothers and their neonates are based on mathematical models. Recently, Das and Mukhopadhyay\cite{16} reported using a mathematical model to study the effects of thyroid function, maternal urinary iodine, and neonatal weights.\cite{16} However, we are aware of no studies based on mathematical models of the effects of iodine on the thyroid function of mothers and their neonates.

To fill this gap in the thyroidological research literature, this study derives the relationship between maternal urinary iodine excretion and the thyroid status of the mothers and their neonates. It
also derives the relationship between the customary measures of the thyroid status of mothers and that of their neonates. This derivation allows the formulation of models that focus on the functional relationships between the maternal urinary iodine and the thyroid status of both mothers and their newborns.

The following sections of this paper cover log-normal and gamma joint generalized linear models, descriptions of the data, covariates, and response. Sections also display analyses and results, interpretation and discussion of the findings, and concluding remarks.

2. JOINT GENERALIZED LINEAR MODELS

Recently, log-normal and gamma models have become of interest in fitting data that arise from physiological studies.\cite{16,17} It is well known that the gamma model with the constant coefficient of variation, and the log-normal model with constant variance, often give similar results.\cite{23} However, in the analysis of physiological data, neither the coefficient of variation nor the variance needs to be constant, so that the two models do not necessarily give similar results.\cite{17}

Das and Lee\cite{18} have shown that for the analysis of data from quality-improvement experiments, the simple log-transformation may not be sufficient for stabilizing the variance. As a result, a further structured dispersion model is required. This, however, results in different optimal settings. Furthermore, with structured dispersion, there is no reason that the two models will give parameterizations with a common interpretation.\cite{18} In general, continuous positive measurements belong to exponential and gamma distributions; they may have variance-to-mean relationship, and the variance of the response is non-constant. For heteroscedastic data, the log-transformation is often recommended for stabilizing the variance,\cite{24} but in practice the variance may not always be stabilized (Myers et al.: Table 2.7).\cite{21,p.36} For example, when

\[ E(Y_i) = \mu_i \quad \text{and} \quad Var(Y_i) = \sigma_i^2 \mu_i^2, \]

the transformation \( Z_i = \log(Y_i) \) gives stabilization of variance \( Var(Z_i) = \sigma_i^2. \)

However, if we want a parsimonious model, we may need a different transformation. Thus, a single data transformation may fail to meet various model assumptions. Nelder and Lee\cite{22} proposed to use joint generalized linear models (JGLMs) for the mean and dispersion.

When the response \( Y_i \) is constrained to be positive, we often use a log transformation \( Z_i = \log Y_i. \) Under the log-normal distribution, we have a joint modeling of the mean and dispersion such that

\[ E(Z_i) = \mu_i, \quad Var(Z_i) = \sigma_i^2, \]

and

\[ \mu_i = x_i^T \beta, \quad \log(\sigma_i^2) = g_i^T \gamma, \]

where \( x_i \) is the row vector for the regression coefficient \( \beta \) in the mean model, and \( g_i \) is the row vector for the regression coefficient \( \gamma \) in the dispersion model.

Lee and Nelder\cite{19} studied the estimation of joint modeling of the mean and dispersion. They proposed to use the maximum likelihood (ML) estimator for the mean parameters \( \beta \) and the re-
stricted maximum likelihood for the dispersion parameters \( \gamma \). The restricted likelihood estimators have proper adjustment of the degrees of freedom by estimating the mean parameters, which is important in the analysis of data from quality-improvement experiments because the number of parameters of \( \beta \) is often relatively large compared with the total sample size.

Nelder and Lee\(^{(22)}\) propose a gamma modelling approach using whole data \( y_i \). They advocate the use of joint generalized linear models:

\[
E(y_i) = \mu_i \quad \text{and} \quad Var(y_i) = \sigma_i^2 V(\mu_i),
\]

where \( V(\cdot) \) is the variance function and \( \sigma_i^2 \)'s are the dispersion parameters. In generalized linear models, the variance consists of two components, \( V(\mu_i) \) is the one depending upon the changes of the mean and \( \sigma_i^2 \) is the one independent of mean adjustment. Instead of defining the two summarizing statistics as responses, they advocate modeling the mean and dispersion parameters jointly as follows:

\[
\eta_i = g(\mu_i) = x_i^T \beta \quad \text{and} \quad \xi_i = h(\sigma_i^2) = w_i^T y_i,
\]

where \( g(\cdot) \) and \( h(\cdot) \) are generalized linear model link functions for the mean and dispersion, respectively and \( x_i^T \) and \( w_i^T \) are the row vectors for regression models based on the levels of control variables. For the estimation they propose to use the maximum likelihood (ML) estimators for the mean model and restricted ML (REML) estimators for the dispersion model.

In generalized linear models, the variance function characterizes the distribution of the generalized linear model family. For example, the distribution is normal if \( V(\mu) = 1 \); Poisson if \( V(\mu) = \mu \); gamma if \( V(\mu) = \mu^2 \); etc. A more extensive discussion of generalized linear model approaches are given in Das and Lee,\(^{[18]}\) Lee and Nelder,\(^{[19,20]}\) Lee et al.\(^{[31]}\) Lesperance and Park,\(^{[14]}\) Qua et al.\(^{[33]}\)

### 3. Data, Covariates, and Responses

Recently, Das and Mukhopadhyay\(^{[16]}\) studied the effects of maternal urinary iodine, the mothers’ and their neonates’ thyroid hormone status, and the neonates’ birth weights. The analyses were based on data collected by Chakraborty et al.,\(^{[25]}\) as are the analyses in this paper. The description of the data set is given in Chakraborty et al.\(^{[25]}\) and Das and Mukhopadhyay.\(^{[16]}\) For ready reference, the study subject data set is as follows:

The data of Chakraborty et al.\(^{[25]}\) is hospital-based, non-interventional, and cross-sectional. The 300 observed pregnant women who were in > 36 weeks of gestation; they were within the reproductive age group of 15-to-45 years. The women were admitted to the Gynaecology and Obstetrics Department of Burdwan Medical College and Hospital, Burdwan, West Bengal, India. Also studied were the respective neonates born to them during one calendar year (from May 2003 to May 2004). This study considered only pregnant women who suffered from iodine deficiency.
Data were collected on 8 variables. These included maternal urinary iodine excretion, $T_3$ ($MT_3$, say) $T_4$ ($MT_4$, say), and TSH ($MTSH$ say). Neonate birth weights ($y$) and their $T_3$ ($CT_3$, say), $T_4$ ($CT_4$, say), ($CTSH$ say) levels were also measured.

Maternal blood was collected from the cubital vein of the forearm for serum TSH assay. The neonatal blood was collected from the umbilical cord for neonatal serum TSH assay. Urinary iodine was assayed in the samples by the wet digestion method based on the 1937 principle of the Sandell and Koltho® reaction\[29\] and the method suggested by Dunn et al.\[30\]

We do not present the data set here, as it would substantially increase the length of the paper. However, we will submit our data set on request for verification of our analysis.

4. Analysis and Results

The aim of this study is the analysis of the relation of maternal urinary iodine to thyroid function test results of both mothers and their neonates. Log-normal and gamma models\[21\] are highly relevant to fitting positive data that arises from quality-improvement experiments. Das and Lee\[18\] have studied positive data for quality-improvement experiments. In doing so, they used log-normal and gamma models with joint generalized linear models. In addition, Das and Mukhopadhyay\[16\] modeled neonatal weights based on log-normal and gamma models. And recently, Das\[17\] studied human biochemical parameters based on log-normal and gamma models.

To understand the relationship of maternal iodine to the mothers’ and their neonates’ thyroid status, we had to derive the following models:

(i) Model of maternal urinary iodine excretion (response) on the mothers’ thyroid hormone and their TSH levels (covariates).

(ii) Model of maternal urinary iodine excretion (response) on neonates’ thyroid hormone and TSH levels (covariates).

(iii) Model of mothers’ thyroid hormone levels.

(iv) Model of neonates’ thyroid hormone levels.

(v) Model of neonatal weights (response) on maternal urinary iodine excretion and mothers’ and her neonates’ thyroid hormone and TSH levels (covariates).\[16\]

We derived first four models above, and the fifth model was derived by Das and Mukhopadhyay.\[16\] These models were derived based on comparisons of log-normal and gamma model. We have selected the best one by comparison of both the models. Log-normal and gamma models are derived based on formulae (2.1) and (2.2), respectively. Final models are displayed, and the comparisons are as in Das and Mukhopadhyay.\[16\]

As noted above, data were collected on 8 variables. These included maternal urinary iodine excretion, $MT_3$, $MT_4$, and $MTSH$, and neonate birth weights ($y$) and their $CT_3$, $CT_4$, $CTSH$. 
Table 1. Results for mean and dispersion models of maternal urinary iodine excretion and her thyroid hormones data from gamma fit (using log link).

<table>
<thead>
<tr>
<th>Covar.</th>
<th>estimate</th>
<th>s.e.</th>
<th>t</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean model</td>
<td>Const.</td>
<td>3.08</td>
<td>0.05</td>
<td>66.83</td>
</tr>
<tr>
<td></td>
<td>MTSH</td>
<td>-0.09</td>
<td>0.01</td>
<td>-8.23</td>
</tr>
<tr>
<td>Dispersion model</td>
<td>Const.</td>
<td>-3.15</td>
<td>0.34</td>
<td>-9.13</td>
</tr>
<tr>
<td></td>
<td>MT$_T$</td>
<td>0.08</td>
<td>0.02</td>
<td>3.36</td>
</tr>
<tr>
<td></td>
<td>MT$_{SH}$</td>
<td>0.15</td>
<td>0.03</td>
<td>5.19</td>
</tr>
</tbody>
</table>

Figure 1. (a) The absolute residual plot with respect to fitted values. (b) The normal probability plot of mean for the non-constant variance models of gamma fit for mothers’ urinary iodine excretion for their thyroid hormone data (Table 1).

4.1. Analysis of Maternal Urinary Iodine on Maternal Thyroid Hormones

In this section we analyze the relationship between maternal urinary iodine excretion data (treated as the response variable) and maternal TSH and thyroid hormones (treated as covariates). We use gamma joint generalized linear models, as in (2.2). Note that for these data, the gamma model fit is better than log-normal fit. The selected models have the smallest Akaike information criterion (AICs) value in each class, as AIC selects a model that minimizes the predicted squared error loss. Results of the analysis are displayed in Table 1.

In Figure 1(a), we plot the absolute values of residuals with respect to fitted values. Figure 1(a) has flat running means, an indication that variance is not increasing with means. In Figure 1(b), we show the normal probability plot for the mean model of our final selected gamma model in Table 1. Figure 1(b) shows no systematic departures, indicating no lack of fit of our final selected models. That there is no missing variable in our fitting is clear from the normal probability plot of the mean model, as there is no gap in this figure. Therefore, the final fitted mean and variance models of the
relation of maternal urinary iodine excretion and maternal TSH and thyroid hormones (from Table 1), respectively, are

\[
\hat{\mu}_{UIE} = \exp(3.08 - 0.09MTSH) \tag{3.1}
\]

and

\[
\hat{\sigma}^2_{UIE} = \exp(-3.15 + 0.08MT + 0.15MTSH) \tag{3.2}
\]

4.2. Analysis of the Relation of Maternal Urinary Iodine to Neonatal Thyroid Hormones

In this section we analyze the relation of maternal urinary iodine excretion (response) data to neonatal TSH and thyroid hormones (covariates). We use gamma joint generalized linear models, as in (2.2). The selected models have the smallest Akaike information criterion (AICs) value in each class. Results of the analysis are presented in Table 2.

In Figure 2(a) and Figure 2(b), we plot, respectively, the absolute values of residuals with respect to fitted values, and the normal probability plot for the mean model of our final selected gamma model in Table 2. Figure 2(a) has flat running means, indicating that the variance is constant under the gamma joint generalized linear model fit. Figure 2(b) presents no lack of fit. Thus, the final fitted mean and variance models of maternal urinary iodine excretion (UIE) on neonatal TSH and thyroid hormones (from Table 2), respectively, are

\[
\hat{\mu}_{UIE} = \exp(2.61 + 0.29CT - 0.02CTSH) \tag{3.3}
\]

and

\[
\hat{\sigma}^2_{UIE} = \exp(-1.55 - 0.55CT + 0.03CTSH) \tag{3.4}
\]

<table>
<thead>
<tr>
<th>Covar.</th>
<th>Estimate</th>
<th>s.e.</th>
<th>(t)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean model</td>
<td>Const.</td>
<td>2.61</td>
<td>0.110</td>
<td>23.62</td>
</tr>
<tr>
<td></td>
<td>(CT_1)</td>
<td>0.29</td>
<td>0.065</td>
<td>4.39</td>
</tr>
<tr>
<td></td>
<td>(CTSH)</td>
<td>-0.02</td>
<td>0.004</td>
<td>-4.59</td>
</tr>
<tr>
<td>Dispers. model</td>
<td>Const.</td>
<td>-1.55</td>
<td>0.314</td>
<td>-4.92</td>
</tr>
<tr>
<td></td>
<td>(CT_3)</td>
<td>-0.55</td>
<td>0.214</td>
<td>-2.57</td>
</tr>
<tr>
<td></td>
<td>(CTSH)</td>
<td>0.03</td>
<td>0.008</td>
<td>4.00</td>
</tr>
</tbody>
</table>

4.3. Analysis of Maternal Thyroid Hormone Status

Das and Mukhopadhyay\(^{(16)}\) have shown that TSH (\(MTSH\) and \(CTSH\), of the maternal and neonatal groups, respectively) has a negative association with \(T_1\) and \(T_4\). They have not derived the relationship among the thyroid components of mother and neonate. This section presents the rela-
tionship between material thyroid hormones, \( MT_i \) and \( MT_j \). We have analyzed the relation of mother \( MTSH \) (response) data to that of maternal thyroid hormones \( MT_i \) and \( MT_j \) (covariates). We used log-normal joint generalized linear models, as in (2.1). Here log-normal gives better fit than gamma fit. The selected models have the smallest Akaike information criterion (AICs) value in each class. The results of the analysis are presented in Table 3.

Figure 2. (a) The absolute residual plot with respect to fitted values. (b) The normal probability plot of mean for the non-constant variance models of gamma fit for maternal urinary iodine excretion in relation to neonatal thyroid hormone data (Table 2).

Figure 3(a) and Figure 3(b), respectively, display the absolute values of residuals with respect to fitted values, and the normal probability plot for the mean model of our final selected log-normal model in Table 3. Figure 3(a) has flat running means, an indication that variance is constant under log-normal joint generalized linear model fit. Figure 3(b) shows no lack of fit. Thus, the final fitted mean and variance models of maternal \( MTSH \) on \( MT_i \) and \( MT_j \) (from Table 3), respectively, are

\[
\hat{\mu}_{MTSH} = \exp(2.77 - 0.26MT_i - 0.12MT_j)
\]

and

\[
\hat{\sigma}^2_{MTSH} = \exp(-3.02 + 0.20MT_j)
\]

Table 3. Results for mean and dispersion models of maternal thyroid hormone data from log-normal fit.

<table>
<thead>
<tr>
<th>Covar.</th>
<th>estimate</th>
<th>s.e.</th>
<th>t</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>Const.</td>
<td>2.77</td>
<td>0.114</td>
<td>24.30</td>
</tr>
<tr>
<td></td>
<td>( MT_i )</td>
<td>-0.26</td>
<td>0.106</td>
<td>-2.46</td>
</tr>
<tr>
<td></td>
<td>( MT_j )</td>
<td>-0.12</td>
<td>0.014</td>
<td>-8.53</td>
</tr>
<tr>
<td>Dispers.</td>
<td>Const.</td>
<td>-3.02</td>
<td>0.237</td>
<td>-12.76</td>
</tr>
<tr>
<td></td>
<td>( MT_i )</td>
<td>0.20</td>
<td>0.023</td>
<td>8.83</td>
</tr>
</tbody>
</table>
4.4. Analysis of Neonatal Thyroid Hormone Status

Relationships among the thyroid hormones of neonates are derived here. We analyzed the relation of neonatal $CTSH$ (response) data to neonatal thyroid hormones, $CT_3$ and $CT_4$, as covariates. We used log-normal joint generalized linear models as in (2.1). Here log-normal gives a better fit than the gamma fit. The selected models have the smallest Akaike information criterion (AICs) value in each class. The results of the analysis are presented in Table 4.

Figure 3. (a) The absolute residual plot with respect to fitted values. (b) The normal probability plot of the means for the non-constant variance models of log-normal fit for maternal thyroid hormone data (Table 3). Figure 4(a) displays the absolute values of residuals with respect to fitted values. Figure 4(b) displays the normal probability plot for the mean model of our final selected log-normal model. Figure 4(a) has flat running means, an indication that variance is constant under the log-normal joint generalized linear model fit. Figure 4(b) shows no lack of fit. Thus, the final fitted mean and variance models of neonatal $CTSH$ on $CT_3$ and $CT_4$ (from Table 4), respectively, are

$$\hat{\mu}_{CTSH} = \exp(4.44 - 0.80CT_3 - 0.18CT_4) \quad (3.7)$$

and

$$\hat{\sigma^2}_{CTSH} = \exp(-1.62 + 0.09CT_4) \quad (3.8)$$

The fitted mean and variance models of neonatal birth weight ($y$), respectively, are
\[ \hat{\mu} = \exp(1.261 - 0.003UIE - 0.031MT_3 - 0.004MT_4 - 0.047CT_3 - 0.007CT_4 + 0.001CTSH) \]  
\[ \hat{\sigma}^2 = \exp(-5.486 + 0.066CT_4) \]  

Table 4. Results for mean and dispersion models of neonatal thyroid hormone data from log-normal fit.

<table>
<thead>
<tr>
<th>Covar.</th>
<th>estimate</th>
<th>s.e.</th>
<th>t</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean model</td>
<td>Const.</td>
<td>4.44</td>
<td>0.112</td>
<td>39.49</td>
</tr>
<tr>
<td></td>
<td>CT_3</td>
<td>-0.80</td>
<td>0.124</td>
<td>-6.49</td>
</tr>
<tr>
<td></td>
<td>CT_4</td>
<td>-0.18</td>
<td>0.018</td>
<td>-9.56</td>
</tr>
<tr>
<td>Dispers. model</td>
<td>Const.</td>
<td>-1.62</td>
<td>0.213</td>
<td>-7.60</td>
</tr>
<tr>
<td></td>
<td>CT_4</td>
<td>0.09</td>
<td>0.028</td>
<td>3.34</td>
</tr>
</tbody>
</table>

Figure 4. (a) The absolute residual plot with respect to fitted values. (b) The normal probability plot of the mean for the non-constant variance models of log-normal fit for neonate thyroid hormone data (Table 4).

5. Findings, Interpretation, and Discussion

This section presents the findings, interpretation, and discussion of our analysis. The following are the major findings.

1. Models (3.1) and (3.2), respectively, represent the mean and variance models of estimated maternal urinary iodine excretion on mothers’ thyroid hormones. From (3.1) it is seen that the estimated mean of urinary iodine excretion is only explained by the statistically significant effect of maternal TSH (i.e., \(MTSH\)). It also shows that estimated mean of maternal urinary iodine excretion has
a negative association with $MTSH$. This means that as urinary iodine excretion decreases, $MTSH$ tends to increase, and vice versa.

On the other hand, (3.5) represents the mean model of $MTSH$. It shows that $MTSH$ has a negative association with both maternal $T_1$ (or $MT_1$) and $T_4$ (or $MT_4$). This means that if $MTSH$ decreases, $MT_1$ and $MT_4$ tend to increase, and vice versa. This means that iodine deficiency hypothyroidism of the mother increases her TSH level. Consequently, maternal $MT_1$ and $MT_4$ tend to decrease, possibly enough to be diagnosed as hypothyroid. In practice, hypothyroidism (i.e., deficiency of iodine intake) results in an enlarged thyroid gland, known as endemic goiter. This condition is recognized as a significant public health issue.\[26\] The research literature indicates that cretinism is associated with endemic goiter.\[26\]

1. If the mother’s iodine intake increases, $MTSH$ decreases, and both the $MT_1$ and $MT_4$ tend to increase. If the respective decreases and increases reach current laboratory criteria, the condition may be diagnosed as hyperthyroidism. The hyperthyroidism may be associated with maternal autoimmune thyroid disease and possibly papillary cancer.\[11\]

2. From (3.2), it is observed that the estimated variance of maternal urinary iodine excretion is positively associated with $MT_1$ and $MTSH$. This indicates that the variance of the estimated maternal urinary iodine excretion increases if $MT_1$ or $MTSH$ or both increase. Also from (3.5), $MT_1$ and $MTSH$ are negatively associated. This indicates that if $MT_1$ increases, $MTSH$ decreases. We always try to estimate mean urinary iodine excretion with small variance.

3. In maternal hypothyroidism, $MTSH$ increases and $MT_1$ decreases. The mother’s urinary iodine excretion decreases and the variance of iodine excretion increases. In maternal hyperthyroidism, $MTSH$ decreases and $MT_1$ increases. Consequently, the mother’s urinary iodine excretion and its variance increase. The estimated variance model (3.2) of maternal urinary iodine excretion does not satisfy the natural relationship of thyroid hormones as in (3.5). This implies that the relationship of iodine to maternal thyroid hormones is complicated, and this suggests that it is important that iodine deficiency corrections be made very accurately.

4. Models (3.3) and (3.4) represent the mean and variance models of estimated maternal urinary iodine excretion in relation to her neonate’s thyroid hormones. In the mean model (3.3), response maternal urinary iodine excretion is associated with the neonate’s $CT_1$ and $CTSH$. The relationships are statistically significant. In the variance model (3.4), estimated variance of maternal urinary iodine excretion is also associated with the neonatal $CT_1$ and $CTSH$. Again, the relationships are statistically significant. Note that in the models (3.3) and (3.4), response is maternal urinary iodine excretion and explanatory variables are the neonate thyroid hormones. This type of response and covariates are rarely observed in clinical practice.

5. From (3.3), it is seen that the estimated mean of maternal urinary iodine excretion has a negative association with neonate $CTSH$ and a positive association with neonate $CT_1$. This implies that as maternal urinary iodine excretion decreases, $CTSH$ increases and $CT_1$ decreases, and vice versa. On the other hand, (3.7) represents the mean model of $CTSH$. It shows that $CTSH$ has a negative association with both $CT_1$ and $CT_2$. This means that if $CTSH$ increases, $CT_1$ and $CT_2$ tend to decrease, and vice versa. This fact supports the model (3.3). Thus, for maternal hypothyroidism due
to iodine deficiency, neonate $CTSH$ increases and $CT_j$ decreases. Consequently, neonate $CT_j$ and $CT_i$ (from model (3.7)) tend to decrease. If the magnitude of these decreases is great enough, the neonate may be diagnosed as hypothyroid. The appropriate conclusion from this is that maternal iodine deficiency may result in hypothyroidism of her neonate. Again, as in serial number 1, it is concluded that iodine deficiency of the mother risks maternal hypothyroidism. Moreover, it also concludes that if the mother suffers from hypothyroidism, her neonate is also at risk of hypothyroidism.

(7) If the mother’s iodine intake increases, the increase may be of a magnitude that leads to a diagnosis of hyperthyroidism. Regardless, the increased maternal iodine results in decreased $CTSH$ and increased $CT_i$. Again from model (3.7), if $CTSH$ decreases, both $CT_i$ and $CT_j$ increase. Thus, when the mother is hyperthyroid, her neonate’s $CTSH$ decreases and his/her $CT_j$ and $CT_i$ increase, possibly leading to neonatal hyperthyroidism. Thus, hyperthyroidism of the mother leads to hyperthyroidism of her neonate (in serial number 2).

(8) From (3.4), it is seen that the estimated variance of maternal urinary iodine excretion has a positive association with neonate $CTSH$ and a negative association with $CT_j$. This indicates that if the variance increases, $CTSH$ tends to increase and $CT_j$ tends to decrease, and vice versa. Again from model (3.7), it is seen that if $CTSH$ increases, $CT_i$ and $CT_j$ decrease, and vice versa. The model (3.4) supports model (3.7). Thus, the estimated variance of maternal urinary iodine excretion has a natural relationship to neonate thyroid hormone levels. We try to estimate the mean with small variance.

(9) From model (3.9), if maternal urinary iodine excretion is very high (hyperthyroidism), neonate $CTSH$ will be low; consequently, neonatal birth weight will be low, and the neonate may die. On the other hand, maternal hypothyroidism from iodine deficiency results in over weight of the neonate (from model (3.9)) and may result in neonatal obesity. It is well known that obesity of neonates affects their brain development. Screening for congenital hypothyroidism, then, offers a useful index of community iodine nutrition and of the risk of brain damage in developing infants. Thus, the risk of brain damage and neonatal mortality, rather than goiter, have become the main reasons for advocating urgent correction of iodine deficiency. Neonates are more sensitive than children and adults to the effects of iodine deficiency because they have a much smaller intrathyroidal iodine pool with markedly accelerated turnover.

6. Concluding Remarks

This paper focuses on the relationships between maternal urinary iodine and the thyroid status of mothers and their neonates. Chakraborty et al. collected the data set used in this analysis. Analysis of the data develops some mathematical models. The models show the relationships of maternal urinary iodine excretion to covariables: maternal thyroid status ($MTSH$ and thyroid hormones, $MT_i, MT_j$); and neonatal thyroid status ($CTSH$ and thyroid hormones, $CT_i, CT_j$).

The derived models are the relationships of (a) maternal urinary iodine excretion to mother’s thyroid hormones; (b) maternal urinary iodine excretion to neonate’s $CT_j$ and $CT_i$; (c) mother’s TSH to $MT_i$ and $MT_j$; and (d) neonate’s TSH to $CT_j$ and $CT_i$. Another model is the relation of neonatal
birth weight to the thyroid status of the mothers and their neonates.\cite{16}

The functional relationships (models through (3.1) to (3.10)) are all non-linear. However, standard errors of the estimates (Table 1 to Table 4) are very small, indicating that the estimates are stable.

The analysis in this paper leads to 9 conclusions that are detailed in Section 5. The conclusions are based on the mathematical models (Section 4) of the relationships of maternal urinary iodine excretion to the thyroid status of the mother and her neonate and neonatal weight. The models support most of the facts observed in clinical practice.

The mathematical models in this report show that the relationships of iodine to the thyroid status of mothers and their neonates are not simple. The models reported here illuminate the complex relationships. Fortunately, a true mathematical model can open the truth that is covered by the complex relationships.

Many parameters have been identified in this analysis as statistically significant in mean and variance models; these models can give a clear picture to practitioners of necessary corrections of iodine levels. The corrections are crucial for pregnant women with thyroid disorders to ensure that they have healthy neonates.

This paper does not focus on iodine in relation to diseases such as goiter, brain damage, and papillary cancer. Nonetheless, human beings can potentially benefit from analysis of these relationships through mathematical models. My subsequent paper will focus on the relation of such diseases to iodine status.

As a final note, it is worth emphasizing that neonates have a smaller intrathyroidal iodine pool and more rapid iodine turnover than adults. Because of this, iodine deficiency risks neonatal brain damage and mortality. These, rather than goiter, have become the main reasons for advocating urgent correction of iodine deficiency.

References


32. Hastie, T., Tibshirani, R., and Friedman, J.: *The


