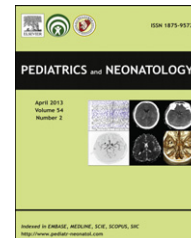




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## CASE REPORT

# Transient Hypothyroidism in Premature Infants After Short-term Topical Iodine Exposure: An Avoidable Risk?<sup>†</sup>

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## Key Words

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Studies in preterm infants have shown that prolonged treatment with topical iodine (multiple doses, often over multiple days) can transiently suppress thyroid function. However, it is uncertain if topical iodine exposure for very short periods of time can cause significant changes in thyroid function. We report two cases of transient hypothyroidism in preterm infants after short-term exposure to topical iodine during surgical preparation, and review their clinical and laboratory findings before and after iodine exposure. We conclude that premature infants are at risk of developing transient hypothyroidism in response to a single, short-term exposure to topical iodine, even in iodine-sufficient geographical areas. We advise monitoring of thyroid function in these infants after iodine exposure, as treatment with levothyroxine may be needed for a limited duration to prevent the sequelae of untreated hypothyroidism. Consideration of using alternative cleansing agents is also advised.

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## 1. Introduction

Transient neonatal hypothyroidism occurs at higher rates in areas of iodine deficiency,<sup>1–3</sup> as well as in infants whose mothers are exposed to large amounts of iodine during pregnancy, at the time of delivery or during lactation.<sup>4–8</sup> Prior studies of preterm infants have shown that prolonged treatment with topical iodine (multiple doses, usually over multiple days) can transiently suppress thyroid function.<sup>9–13</sup> However there is still uncertainty as to whether topical iodine exposure for very short periods of time can cause significant changes in thyroid function in premature infants, with some studies suggesting that such exposure does not alter thyroid-stimulating hormone (TSH) in infants born in iodine-replete areas.<sup>14,15</sup> We report two cases of transient hypothyroidism in preterm infants, both born in iodine-replete areas, with a significant rise in TSH after short-term exposure to iodine during surgical preparation.

## 2. Case Reports

### 2.1. Case 1

A 27-week estimated gestational age (EGA) female with multiple congenital anomalies including tracheo-esophageal (TE) fistula with esophageal atresia had initial newborn screening tests at 48 hours that showed a low total T<sub>4</sub> of 68.2 nmol/L but a normal TSH of 1.9 uIU/mL. Repair of the TE fistula and gastrostomy-tube placement was performed the next day. The infant was exposed to 10% povidone-iodine solution (Betadine) applied topically to the abdomen and chest for 2.5 hours for surgical preparation.

A second newborn screening test obtained on Day 12 of life revealed hypothyroidism, with a subsequent confirmatory serum sample showing a TSH > 150 uIU/mL and free T<sub>4</sub> (FT<sub>4</sub>) of 3.86 pmol/L. Treatment was started with levothyroxine, and 7 days later, the TSH normalized. Treatment was ultimately discontinued by 10 weeks of age.

### 2.2. Case 2

A 32-week EGA female was found prenatally to have a congenital diaphragmatic hernia (CDH) and resulting hydrops. Initial newborn screening tests obtained at 48 hours showed a low total T<sub>4</sub> of 34.8 nmol/L with a TSH of 10 uIU/mL. Open repair of the diaphragmatic hernia was performed on Day 5 of life, where the infant was exposed to 10% povidone-iodine solution (Betadine) applied topically

to the abdomen and chest for 90 minutes. All iodine was promptly removed after completion of the surgery.

Follow-up newborn screening tests performed at 2 weeks of age, 8 days after surgery, demonstrated hypothyroidism. Subsequent confirmatory serum testing showed a TSH of 391 uIU/mL and FT<sub>4</sub> of 1.42 pmol/L. Treatment with levothyroxine rapidly normalized the TSH within 2 weeks. Thyroid ultrasound confirmed a normal location and size for the thyroid gland. Because of the patient's age, it was decided to continue treatment with 25 µg levothyroxine daily with close follow-up of her thyroid function tests.

A detailed time course of laboratory results, treatment doses and demographic information for both patients are summarized in Table 1.

## 3. Discussion

Exposure to exogenous iodine induces a reflexic response in the thyroid axis of the preterm infant via the Wolff–Chaikoff effect. This effect, a protective autoregulatory mechanism that inhibits formation of thyroid hormone in response to elevated levels of circulating iodide, typically resolves in a few days to weeks.<sup>10</sup> This most often occurs in response to oral iodine treatment or parenteral exposure from contrast agents and is not usually a cause of concern for patients exposed only to topical iodine.

Povidone-iodine solution is a commonly used topical antiseptic and is very effective in preventing infection. Although repeated exposure to topical iodine (repeated applications continued for greater than a few days) have been reported to alter thyroid function in premature neonates,<sup>9–13</sup> it is still unclear if short-term or even a single exposure to topical iodine can significantly alter thyroid function in this population. Premature infants have a very thin epidermis that may result in greater iodine absorption and a thyroid axis that is very sensitive to the inhibitory effects of iodine overload. These features result in delayed escape of inhibition of thyroid hormone synthesis, increasing the likelihood of exogenous iodine toxicity.<sup>16</sup>

Although prior studies have examined this issue, there is still considerable uncertainty surrounding the frequency and duration of iodine exposure necessary to cause hypothyroidism in this population. A prospective study in Italy, which is a relatively iodine-deficient area, showed that if topical iodine is left on the skin of very-low-birth-weight infants at the site of minor procedures and is not cleaned off until routine cleaning of the infant is done later, then the TSH can rise to as high as 60 uIU/mL.<sup>17</sup> A similar study showed that routine use of iodine for procedures such as

**Table 1** Laboratory values throughout the clinical course.

	Birth weight (g)	EGA (wk)	TSH (uIU/mL)/T <sub>4</sub> (nmol/L)		TSH (uIU/mL)/FT <sub>4</sub> (pmol/L)		Therapy
			On first newborn screen	On second newborn screen	Confirmatory labs	Shortly after initiating treatment	
Case 1	916	27 + 6	1.9/68.2	39.8/18.0	>150/3.86	1.0/19.3	Stopped at 10 wk
Case 2	2300	32 + 0	10/34.8	287/13.5	391/1.42	1.5/28.3	25 µg QD

EGA = estimated gestational age; FT<sub>4</sub> = free T<sub>4</sub>; QD = once daily; TSH = thyroid-stimulating hormone.

insertion of intravenous lines and blood gas determination can cause TSH to rise to as high as 20 uIU/mL, but the precise duration of iodine exposure for each infant affected in this study was not reported.<sup>18</sup> In contrast, a prospective study by Brown et al disputed this finding, showing that although urinary iodine excretion was increased in premature infants exposed to topical iodine for skin cleaning prior to routine procedures, serum TSH did not rise, presumably because the North American population studied was iodine-sufficient.<sup>14</sup> Two other studies have also shown that increased urinary iodine concentration was not linked to transient neonatal hypothyroidism.<sup>15,19</sup> Unfortunately, the issue of iodine sufficiency during pregnancy has not been resolved, and in fact, recent reports show that inadequate iodine intake during pregnancy is increasing in many parts of the world, potentially putting the newborns of these mothers at risk for transient hypothyroidism as a result of maternal iodine deficiency.<sup>20</sup>

Premature infants are not the only population at risk of hypothyroidism secondary to iodine exposure. Term neonates can also show a rise in TSH when exposed to large amounts of iodine, as has been reported in infants undergoing cardiac catheterization and surgical repair for congenital heart disease. These infants are exposed to both intravenous iodinated contrast studies and topical iodine, with some infants needing treatment with levothyroxine for up to 10 months.<sup>21</sup>

In our cases described above, we found that topical exposure to iodine for only 90–150 minutes, which was immediately cleaned off at the completion of the procedure, was enough to cause a rise in TSH to nearly 400 uIU/mL in premature infants who did not have elevation of TSH on their initial thyroid screening tests. In both cases, the infants were undergoing surgery that required a large field of preparation.

We feel it is important to report these findings for two reasons. First, while primary hypothyroidism has been reported in patients with CDH and in patients with esophageal atresia,<sup>22–24</sup> our patients show that a single exposure to topical iodine may be associated with transient hypothyroidism and that active surveillance is required in order to discover and properly manage this condition. Premature infants are at high risk of neuro-developmental delays for multiple reasons, and every effort should be made to decrease potential contributing factors. One could argue that the acquired hypothyroidism was transient, and may have been relatively brief, with little impact. However, in both of these cases, the rise in TSH was quite robust (391 and >150 uIU/mL, respectively), suggesting that the reduced levels of thyroid hormone could have had negative consequence on neurocognitive outcome.<sup>25</sup> Had these findings not been discovered by mandated repeated newborn screening because of the initial low T<sub>4</sub> values commonly seen in preterm infants, they may have remained untreated for an extended period of time. In areas of the USA, or other parts of the world, where repeat newborn screening is not mandatory, increased vigilance to follow serial thyroid function testing for infants exposed to topical iodine is suggested in an effort to identify and initiate thyroid hormone replacement as quickly as possible.

Second, these cases highlight that consideration should be given to reducing the amount of iodine used during

procedures on premature infants. Alternative agents are available, such as the alcohol-based cleansers 2% chlorhexidine gluconate and 70% isopropyl alcohol (ChlorPrep) and 4% chlorhexidine gluconate and 4% isopropyl alcohol (Hibiclens). In adults, these alcohol-based cleansing agents have been shown to be more efficacious in reducing postoperative infections.<sup>26</sup> However, in premature infants, these agents must be used cautiously because of the increased risk of systemic absorption and skin irritation. In addition, these agents are more transparent and the extent of preparation may not be easily visualized, potentially putting the patient at a risk for infection or toxicity.

Both infants described above were born in an iodine-sufficient region of the world and were in neonatal intensive care units that use alcohol-based cleansers, not iodine, for routine skin cleaning. They were not exposed to iodine for wound care, nor did they receive any significant exposure to topical iodine from other procedures. However, when they were brought to the operating room for their procedure, iodine preparation was used. From this, we conclude that preterm infants who are exposed to topical iodine over a large area may be at risk of developing transient hypothyroidism, even after a single exposure. We advise monitoring of thyroid function in these infants, as this may lead to early treatment and prevention of the potential sequelae of untreated hypothyroidism. Once treatment is initiated, thyroid function must be followed closely to ensure that thyroid hormone replacement therapy is stopped once the transient hypothyroidism has resolved. Lastly, prevention may be the best approach, with consideration of replacing iodine-containing topical cleansing solutions with effective alternatives when available.

#### 4. Conclusion

Premature infants are at risk of developing transient hypothyroidism in response to a single, short-term topical iodine exposure, even in iodine-sufficient geographic areas. Therefore we advise monitoring of thyroid function in these infants after iodine exposure, as treatment with levothyroxine may be needed for a limited duration to prevent the sequelae of untreated hypothyroidism.

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