DOI: 10.4274/jcrpe.galenos.2024.2023-12-2

Brief Report

Iodinated Contrast Induced Hypothyroidism in the Infant After Enteral Contrast Enema: A Case Report and Systematic Review

Pijpers AGH et al. Iodinated Contrast Induced Hypothyroidism in Infants

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What is already known on this topic?
Knowledge on the effects of iodinated contrast media (ICM) on thyroid function in children is scarce. After the FDA warning on the use of ICM in 2022 this topic raised more attention. Most studies focused on the effect of topical or intravascular administration of ICM on thyroid function. However, data on the effect of enteral ICM administration on thyroid function are lacking.

What does this study add?
This is the first study that provides a systematic review of the current literature on enteral ICM induced hypothyroidism in infants. The case-report and overview of the available literature illustrates the potential severity of iodinated contrast induced hypothyroidism and underlines the necessity of future studies and clinical guidelines on this topic.

Abstract
Background: Excessive iodine intake triggers the Wolff-Chaikoff effect resulting in downregulation of thyroid hormone synthesis to prevent hyperthyroidism. Failure to escape the Wolff-Chaikoff effect can be seen especially in (premature born) infants and may result in prolonged iodine induced hypothyroidism. We describe a rare case of a preterm infant who developed severe iodinated contrast induced hypothyroidism after the use and prolonged stasis of enteral iodinated contrast media (ICM). In addition a systematic literature search was performed to evaluate all available data on this complication.
Methods: A systematic literature search was performed in PubMed and Embase. Studies describing the effect of enteral ICM on thyroid function were considered eligible. The primary outcome was to determine the frequency of contrast induced hypothyroidism in infants after administration of enteral ICM.
Results: The premature infant in our center developed severe iodinated contrast induced hypothyroidism after enteral ICM. In total, only two studies met our eligibility data, reporting eight patients. Out of these eight patients, four premature infants developed a contrast induced hypothyroidism after enteral administration of ICM.
Conclusion: Data on severity, length and frequency of contrast induced hypothyroidism after exposure to enteral ICM is very scarce. The herein reported case and literature search illustrate the potential severity of the complication and underline the necessity of future studies on this topic. We recommend standardized monitoring of thyroid function after exposure to enteral ICM in newborns to prevent delayed diagnosis of severe contrast induced hypothyroidism until evidence based recommendations can be made.
Keywords: Hypothyroidism, iodinated contrast media, contrast induced hypothyroidism

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13.03.2023
17.08.2024

Published: 27.08.2024

Introduction
Thyroid hormones are essential in intrauterine and postnatal brain development, growth and metabolism [1]. Untreated persistent neonatal hypothyroidism can cause serious brain damage, including mental retardation and impaired motor function [1]. Therefore, newborn screening (NBS) programs for congenital hypothyroidism (CH) are in place to detect thyroid dysfunction as early as possible in life and to prevent brain damage by timely start of levothyroxine treatment [2]. Depending on the type of NBS program, only primary CH, or primary and central CH can be diagnosed. Primary CH is caused by abnormal thyroid gland development or thyroid hormone biosynthesis, with an estimated incidence of 1:3000-4000 live births [3].
Acquired hypothyroidism in the neonatal period is rare. One of its potential causes is the excessive exposure to iodine via the skin (disinfectants/antiseptics containing iodine), gastrointestinal tract or intravenously (iodinated contrast medium; ICM) [4-7]. Iodine is crucial for

thyroid hormone synthesis. Many radiological diagnostic procedures involve ICM, resulting in potential excessive iodine exposure to the thyroid gland. Physiologically, the thyroid responds with downregulation of thyroid hormone synthesis to prevent hyperthyroidism, a phenomenon called the Wolff-Chaikoff effect [8]. After a few days to weeks escape from the Wolff-Chaikoff effect should occur, resulting in normalization of thyroid hormone synthesis. However, failure to escape the effect may result in prolonged hypothyroidism. Previous studies have shown that both topical and intravenous ICM administration can cause transient thyroid dysfunction, particularly in preterm infants as a result of a failed escape [9-11]. It is thought that prematurity is a risk factor for prolonged hypothyroidism after exposure to ICM because of immaturity of the escape mechanism [12]. Especially during the neonatal period, when brain development is dependent on sufficient thyroid hormone concentrations, prolonged hypothyroidism should be prevented.

In 2022, the United States Food and Drug Administration (FDA) released a medication safety communication recommending thyroid function evaluation for children under the age of three years within three weeks after intravascular administration of ICM [12]. The FDA statement resulted in increased attention to this subject. Subsequently, the Pediatric Endocrine Society (PES) and American College of Radiology (ACR) published statements questioning this recommendation due to lack of evidence and proposed a more individualized approach, identifying high-risk patient groups, like premature newborns [2,5]. The current recommendations address intravenous ICM administration and overlook enteral ICM administration. Here we describe a case of prolonged hypothyroidism in a premature infant after enteral ICM exposure, and summarize the results of a systematic literature study into the reported number of contrast induced hypothyroidism in infants after enteral ICM administration.

Methods

A literature study was conducted according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines. In accordance with the guidelines, our systematic review protocol was registered in the International prospective register of systematic reviews (PROSPERO) with the number CRD42023393923. Informed consent was obtained from parents of the patient that is described in the case-report. Ethical committee approval was not required for this study.

Literature search

All scientific publications reporting on enteral ICM administration in newborns were considered eligible for review. A medical information specialist (RdV) searched electronic databases (PubMed and EmBase) from inception to January 23, 2023. The following terms were used (including synonyms and closely related words) as index terms or free-text words: “Iodinated contrast media”, “Thyroid function”, “Hypothyroidism” and “Neonates”. Language restrictions were not applied and duplicates were excluded by RvD using Endnote X20.0.1 (Clarivate^{tm}), following the Amsterdam Efficient Deduplication (AED) and Bramer-methods [13]. Studies were screened by two independent authors using Rayyan (LDES, AGHP) [14]. Full texts of the selected articles were retrieved for further review. Any disagreements were resolved by consultation with an expert specialist (JPMD). The reference lists of included articles were reviewed for additional relevant studies. Inclusion criteria were pediatric patients under the age of one year, enteral administered ICM and clearly described follow-up of thyroid function. Animal studies, duplicates, conference abstracts, studies reporting on intravenous or topical ICM administration and previous published data were excluded. The full search strategies for all databases are available as supplementary material.

Primary outcome

The primary outcome was to determine the reported number of contrast induced hypothyroidism in infants after enteral administration of ICM. This outcome was illustrated with a case-report from our own center.

Data extraction and validity assessment

Two authors (LDES, AGHP) independently extracted the data, and evaluated the methodological quality and risk of bias. Disagreements were resolved through discussion; if no consensus could be reached, a third reviewer was consulted (JPMD).

All included articles were assessed for methodological quality and risk of bias using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case-reports, Case series and cohort studies [15]. For each tool several questions regarding methodological quality of the study need to be answered with “Yes”, “No”, “Unclear” or “Not applicable”. Each answer option was scored and summed up. The maximum score for case-reports was 24 points. “High” quality was defined as 19 points or higher, “Moderate” as 14 to 18 points, and “Low” as 13 points or lower. For case series the maximum score was 30 points. “High” quality was defined as 24 points or higher, “Moderate” as 17 to 23, and “Low” as 16 points or less. Publications scored as “high” or “moderate” quality were included in this systematic review.

Statistical analysis

Statistical meta-analysis of data obtained in the systematic review was not performed due to the low number of included articles.

Results

1. Case-report

The patient is a girl, born small for gestational age through cesarean section at gestational age of $26^{6}/_{7}$ weeks (birthweight 550 g, Z-score -1.7) [16]. The pregnancy was complicated by fetal growth restriction due to placental insufficiency. Prenatal fetal ultrasound revealed dilated intestinal loops. The first weeks of life were complicated by multiple gastro-intestinal problems including meconium plug requiring ileostomy creation on day 2 (D2), and a jejunal intestinal perforation on D6 for which surgery was performed with overstitching of the perforation (Figure 1). Postoperatively, on D8 minimal enteral feeding was started. However, an increase in feeding volumes resulted in a high-output stoma. Additionally, failure to grow and difficulties with distal stoma refeeding were observed. A fistulogram was performed on D79 using 20 ml of omnipaque (240 mg I/ml) to visualize the distal bowel patency, showing no stenosis, obstruction or dilated bowel loops (Figure 2A). Surgical stoma reversal was done on D85. Postoperatively, bilious retentions persisted and there was no defecation. The patient developed a severe systemic inflammatory response syndrome (SIRS), resulting in respiratory insufficiency requiring high respiratory pressures, hypotension, electrolyte imbalances, and extreme soft tissue edemas necessitating circulatory support (Figure 2B). The chest X-ray on D95 showed ICM stasis in the rectum (Figure 2C). Rectal irrigation was started on D98 due to constipation. On D98 a chest X-ray was made to check for pulmonary abnormalities, showing signs of osteopenia (Figure 2D). With no clear cause for the clinical deterioration, the pediatric endocrinologist was consulted regarding the osteopenia and suspicion of adrenal insufficiency as a possible cause of the circulatory insufficiency. Central adrenal insufficiency was ruled out via a low-dose cosyntropin stimulation test. Additional endocrinological laboratory test on D99 revealed severe primary hypothyroidism with an extremely elevated thyroid-stimulating hormone (TSH) level of 740 mU/L (local age-specific reference range 0.7-8.4 mU/L) and very low FT4 level of 2.8 pmol/L (local age-specific reference range 11.9-25.6 pmol/L). Prior to this, the NBS result for CH was normal, as were previous thyroid function tests (FT4 concentration 15.0 pmol/L at D58). Treatment with levothyroxine was started immediately (D99) in a daily dose of 25 mcg (6.62 mcg/kg/day). Within two days after start of levothyroxine treatment, circulatory and respiratory status improved and treatment with inotropic drugs could be stopped. During follow-up, levothyroxine dose was titrated based on thyroid function testing. At D264 levothyroxine treatment could be stopped with normal thyroid function at further follow-up.

The girl’s primary hypothyroidism was thought to be acquired, especially because of the normal FT4 concentration at D58. In retrospect, the ICM administered on D79 was still visible on the chest X-ray on D95, indicating gastro-intestinal stasis of ICM for 19 days. This prolonged exposure

to ICM was judged as the most likely cause of the hypothyroidism. Since iodine-induced hypothyroidism is basically a transient problem, the fact that the thyroid function remained normal after stopping levothyroxine treatment is further proof for this diagnosis.

2. Systematic review

The systematic literature search in PubMed and Embase resulted in 2012 unique articles. After title and abstract screening 1984 articles were excluded. The remaining 28 articles underwent full-text screening, resulting in exlusion of 26 articles. Reasons for exclusion were intravenous contrast administration (n=12), topical povidone use (n=4), studies without original data (n=9), and incomplete information (n=1). Ultimately, two studies were included, reporting eight patients with thyroid function follow-up after exposure to iodinated enteral contrast enema (Figure 3). Study characteristics are summarized in Table 1 [17,18].

Risk of bias

Risk of bias was assessed using the JBI Critical Appraisal Checklist for case-reports, case series and cohort studies [15]. Results are shown in table 2 of the supplementary materials. The quality of the case-report by Lombard et al. was scored as high [18] and the case series of Ares et al. was scored as moderate [17].

Study characteristics of contrast induced hypothyroidism.

The two eligible studies, published in 2008 and 2009, included one case-series and one case-report. The case series of Ares et al. described seven newborns from a neonatology department during a one-year period. The infants received Gastrografin, a contrast enema with an iodine concentration of 370 mg/ml [17]. The indication for Gastrografin administration was treatment for uncomplicated meconium ileus in three patients, and use as contrast medium for radiological imaging in four patients. All had normal NBS results for CH. Six out of seven patients were born preterm (range 27-36 weeks gestational age). Hypothyroidism was defined as increased TSH levels (local reference range 0.5-6.15 mU/L) and normal to decreased FT4 levels (local reference range 0.70-1.64 µg/dl). Normal total T4 levels were defined as >6.5 µg/dl. Three of the seven reported patients developed contrast induced hypothyroidism (Table 1). All three patients with hypothyroidism were born premature. The first diagnosed patient was treated with Gastrografin for meconium ileus; revealing elevated TSH levels and decreased FT4 levels on D6 after administration. In the second case, Gastrografin was administered as contrast enema, resulting in increased TSH and normal FT4 levels observed 13 days later. In the third case, Gastrografin was administered as contrast media. TSH levels were increased, but the total T4 level was elevated. The duration between Gastrografin administration and thyroid function evaluation was not specified. The three infants diagnosed with contrast induced hypothyroidism were all treated with levothyroxine for one month after which levothyroxine treatment was stopped. In one patient the TSH level was high after cessation of levothyroxine treatment resulting in restarting levothyroxine treatment and further follow-up by a pediatric endocrinologist. In summary, Ares et al. reported that three out of seven infants who received Gastrografin, all premature born, were diagnosed with, and treated for iodine induced hypothyroidism.

Lombard et al. reported a case-report of a male infant, born at 27 weeks gestation. Due to failure to pass stools, he underwent a diagnostic test receiving a sodium ioxitalamate contrast enema with an iodine concentration of 120 mg/ml (less than 20 ml). After 23 days the male infant developed jaundice and biochemical evaluation showed cholestasis. Sixty-six days after contrast administration thyroid function was evaluated because of persistent cholestasis. Contrast induced hypothyroidism was diagnosed based on elevated TSH, decreased FT4 and normal FT3 levels (Table 1). Treatment with levothyroxine was started immediately. After 49 days treatment could be stopped, and TSH, FT4 and FT3 levels remained normal.

In total, four of the eight reported patients who received enteral ICM were diagnosed with contrast induced hypothyroidism. The patients with reported iodinated contrast induced hypothyroidism were all born premature.

Discussion

We present a case of a preterm infant who developed iodine induced hypothyroidism after enteral ICM administration via a fistulogram, followed by prolonged stasis of the ICM. Within twenty days after ICM administration the patient developed severe SIRS. Laboratory results showed an extremely elevated TSH level and a very low FT4, indicating severe primary hypothyroidism. Although it is uncertain whether the clinical symptoms prior to levothyroxine treatment were only caused by severe hypothyroidism, the patient recovered rapidly after initiation of treatment with levothyroxine. A systematic literature search was performed to evaluate this complication of enteral ICM. Only two studies reported on iodine induced hypothyroidism after enteral ICM administration, including eight patients of which four were diagnosed with ICM induced hypothyroidism.

The FDA released a medication safety communication in March 2022 advising thyroid function monitoring within three weeks following intravascular administration of ICM in all children under the age of three years [12]. This caution is rooted in the fact that especially infants are vulnerable to thyroid dysfunction after excessive intake of iodine resulting in the Wolff-Chaikoff effect [8]. The escape from the inhibitory impact of high iodine dosages, however, is not always successful in infants, and may cause clinical or subclinical hypothyroidism [19]. It is thought that especially preterm infants might be at risk to develop ICM induced hypothyroidism since the ability to escape from the Wolff-Chaikoff effect develops only between 36 and 40 weeks of gestation [20,21]. Effects of ICM administration on thyroid function in children has therefore been a topic of debate in recent literature. Available literature primarily focused on intravenous administration (e.g., for cardiac interventions and evaluation of tip position of peripherally inserted central catheter (PICC)) or topical administration (e.g., disinfectants) [4,9,22]. The results of these studies are contradicting and randomized studies with large sample sizes are lacking. The results of our systematic literature search show that evidence on the effects of the use of enteral ICM in (premature) infants on thyroid function is limited. Nevertheless, it is important to raise awareness for the potential severe clinical consequences of late diagnosis of iodine induced hypothyroidism after prolonged exposure to enteral ICM as illustrated by our patient.

In patients with CH it is known that persistent low thyroid hormones concentrations have a major negative impact on brain development. Over the last decades, more and more countries introduced NBS for CH. Since then, numerous studies have sought to compare the IQ scores of patients treated for CH with those who received no treatment. The benefits of early detection and treatment are indisputable from these studies [23,24]. Notably, subsequent studies have found that the severity of hypothyroidism plays a significant role in the neurological outcome of these patients [3]. In cases with acquired hypothyroidism, such as patients with contrast induced hypothyroidism, the period of low thyroid hormones is relatively short and transient. However, one may hypothesize that especially in (preterm) infants, even a relatively short period of severe hypothyroidism could negatively impact brain development with potential lifelong consequences.

We speculate that prolonged enteral exposure to ICM may result in increased iodine uptake, although it is unknown if intestinal permeability, the duration of stasis or the amount and concentration of the ICM contrast plays a role in development of hypothyroidism. Our case illustrated that the contrast remained in the bowel until rectal irrigation, nineteen days after fistulogram. The higher the iodine exposure, the likelier it is that the Wolff-Chaikoff effect occurs. As stated previously, especially premature infants are more vulnerable for failure to escape the inhibitory Wolff-Chaikoff effect, resulting in prolonged thyroid dysfunction. Therefore, stasis of ICM may be one of the risk factors contributing to the development of contrast induced hypothyroidism.

Following the reported recent case in our center, speculation arose regarding the severity, length and frequency of this complication in infants since thyroid function monitoring was not standard care for those receiving enteral ICM. The results of the literature review showed only two previous publications describing four infants suffering from contrast induced hypothyroidism. However, the potential complication of enteral ICM induced hypothyroidism have been reported in additional publications that were not included in our systematic review due to incomplete data [9,25-28]. It has been suggested in some of these publications that monitoring of thyroid function after enteral administration of ICM is wanted until an evidence based guideline is available, as is stated by the PES and ACR as well [27,28]. Although overall evidence is limited, the available data suggests that contrast induced hypothyroidism might be a more frequent complication after the use of enteral ICM then previously realized. Consequently, a local protocol was implemented as standard care in our hospital, consisting of standard testing of the thyroid function and abdominal X-rays to detect stasis of contrast in infants after enteral ICM administration.

Limitations

This case-report and systematic review aimed to provide insights into the clinical presentation of iodine induced hypothyroidism in infants following enteral ICM administration. However, several limitations must be acknowledged. The finding of this case-report might be specific to the individual patient described and may not be applicable to a broader population or different clinical setting. In addition, the urinary iodine excretion was measured 26 days after enteral ICM administration. At that time, urinary iodine levels were not elevated. However, we believe that urinary iodine levels would have been high shortly after (prolonged) enteral exposure to ICM. In retrospect, earlier evaluation of urinary iodine excretion could have confirmed systemic exposure to high levels of iodine. The systematic review's primary limitation is that none of the included studies specifically focused on the occurrence of contrast induced hypothyroidism in infants. Furthermore, publication bias could impact results, as unreported negative cases make determining the number of contrast induced hypothyroidism challenging. Nevertheless, this is the first systematic review reporting on the effect of enteral ICM on thyroid function in infants.

Conclusion

We present a unique case-report of contrast induced hypothyroidism after prolonged stasis of administered enteral ICM in a premature infant. Additional studies on the severity, length and frequency of this complication are lacking as our systematic review only identified two studies reporting on enteral ICM induced hypothyroidism with a very small sample size. Therefore we are unable to report a true number of contrast induced hypothyroidism in infants who were exposed to enteral ICM. In line with the PES and ACR statements, we recommend monitoring of thyroid function after the use of enteral ICM in (preterm) infants until an evidence based guideline is available.

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Figure 1 - Timeline of a neonatal patient who developed iodinated contrast induced hypothyroidism.

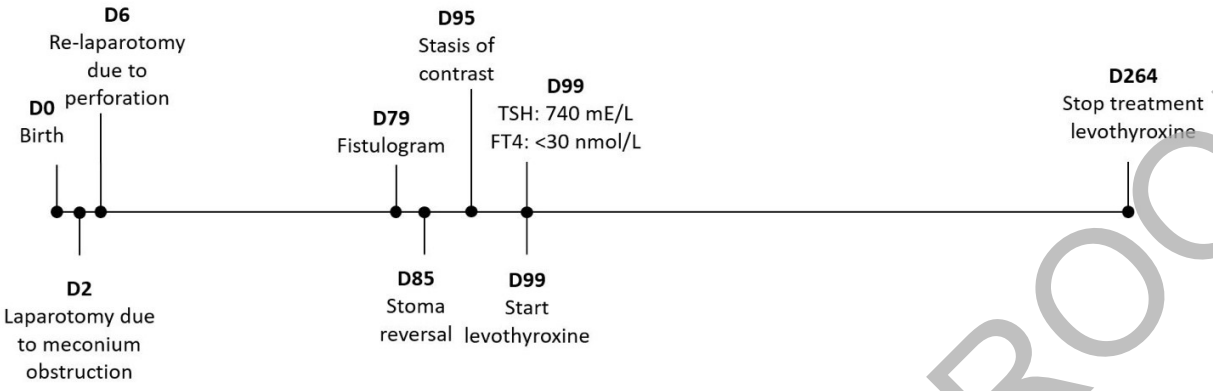

Figure 2 - Radiological images of a neonatal patient who developed iodinated contrast induced hypothyroidism.
A: D79, fistulogram. Contrast enema omnipaque 240 mg I/ml, 20ml administered via the ileostomy. Normal diameter and appearance of the bowel loops and colon.
B: D86, X-ray of the thorax and abdomen. Seven days after contrast enema. Pulmonary markings that indicate bronchopulmonary dysplasia. Distended abdomen, with abnormal bowel gas, and residual intraluminal contrast in the distal recto sigmoid. Edematous soft tissue.
C: D95, X-ray of the thorax and abdomen. Sixteen days after contrast enema, still intraluminal contrast visible.
D: D98, X-ray of the thorax and abdomen. Nineteen days after contrast enema. After rectal irrigation. Only subtle intraluminal contrast visible.

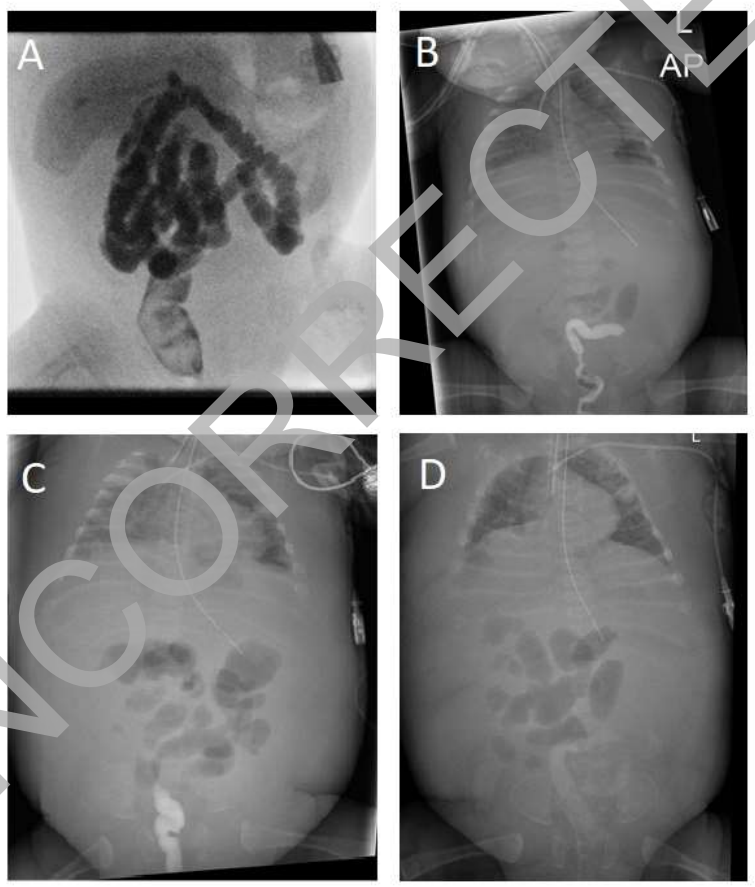

Figure 3 – Flowchart of search and selection process.

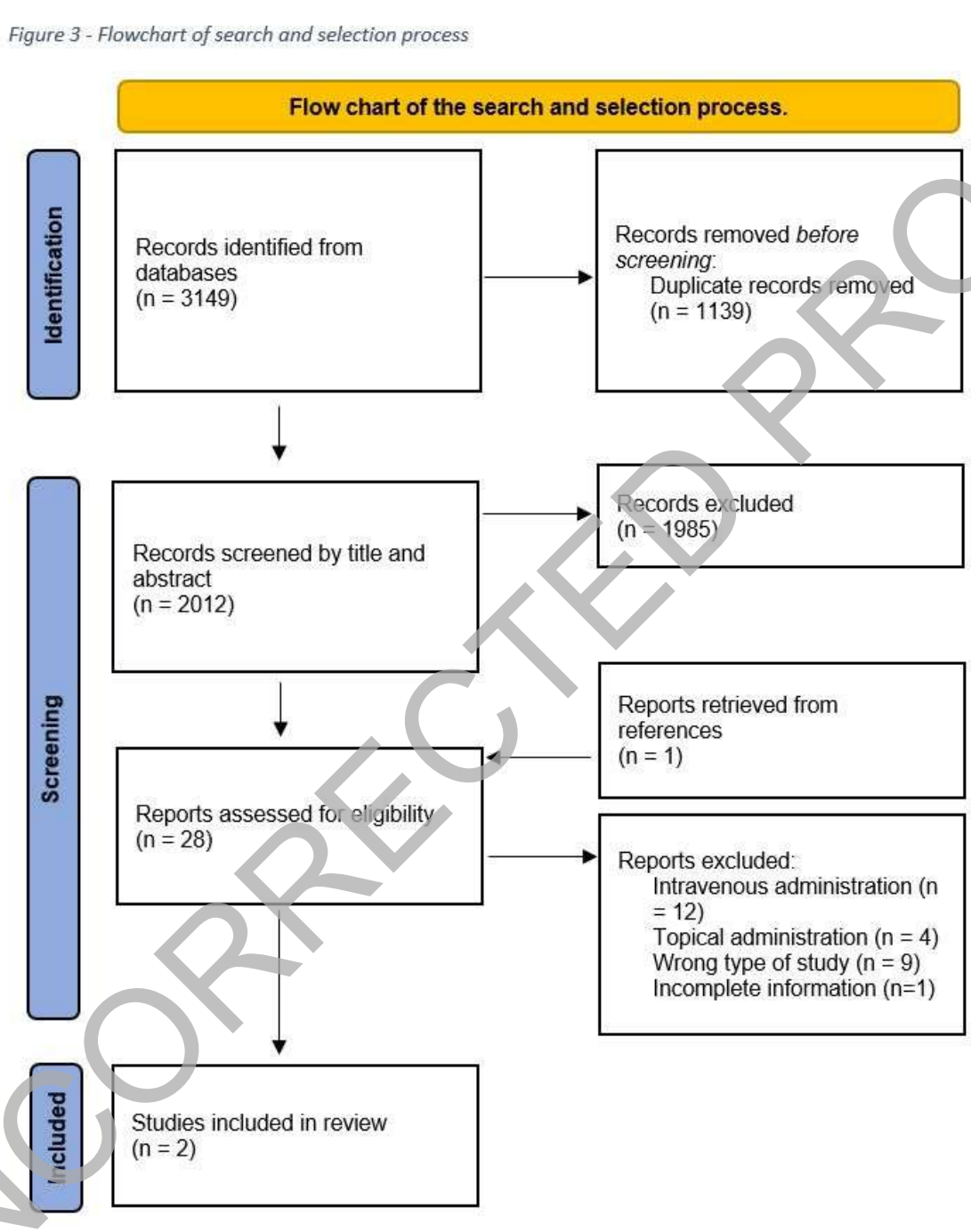

Table 1 – Included studies in this systematic review on contrast induced hypothyroidism in neonates

Author	Year	Type of study	Premature	CIH	Type of contrast	Reason for use of iodinated enteral contrast	Laboratory values	Treatment levothyroxine
Ares et al.[17]	2008	Case-series	6/7, range 27-36 weeks GA	3/7	Gastrografin	3 treatment uncomplicated meconium obstruction 4 radiological imaging	*Case 1* TSH: 33.14 µUI/ml FT4: 0.51 µg/dl *Case 2* TSH: 25.7 µUI/ml FT4: 1.06 µg/dl *Case 3* TSH: 40.0 µUI/ml total T4: 3.4 µg/dl	3/7
Lombard et al.[18]	2009	Case-report	1/1, 27 weeks GA	1/1	Ioxitamalate (telebrix 12)	1 meconium obstruction	TSH: 368 µUI/ml (local reference range 0.2-4.2 µUI/ml), FT4: 5.1 pg/ml (local reference range 9.3-17.0 pg/ml) FT3: 2 pg/ml (local reference 1.5-4.1 pg/ml)	1/1