

Iodine and fertility: do we know enough?

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ABSTRACT: Iodine is a vital micronutrient and its importance in thyroid function is well established. However, abnormalities in iodine intake may also have other effects. In particular, iodine is taken up avidly by the ovary and endometrium. Iodine deficiency is associated with reduced fertility. The use of high iodine concentration contrast media has recently been shown to improve conception rates in couples with unexplained infertility (UI). We hypothesize that this improvement could be related to the iodine excess and mechanisms independent of its action on thyroid. In this article, the metabolism of iodine and its potential role in fertility will be discussed, including the impact of both iodine deficiency and excess states and the importance of iodine in normal fetal development. This will include insights from animal studies on the effect of iodine in the uterine and ovarian structural environment, hormonal milieu and immunological factors affecting implantation. We speculate that iodine may well have a role as a potential therapy for UI.

Key words: unexplained infertility / iodine / lipiodol / oil-soluble contrast / endometriosis / fertility

Introduction

Iodine is an essential micronutrient necessary for normal reproductive function and fetal wellbeing. Iodine deficiency is associated with increased maternal and perinatal morbidities, while excess iodine is also detrimental during pregnancy. This mini-review discusses the impact of iodine deficiency and excess on normal reproductive function. In particular, we discuss the potential role of iodine excess in the treatment of infertility.

Iodine—an essential micronutrient for normal reproduction

Iodine is a trace element in soil and water and is ingested in several chemical forms. Seaweeds, fish or other seafood, iodized salt and iodinated breads are the main dietary sources of iodine (Leung and Braverman, 2014). Most forms of iodine are reduced to iodide and efficiently absorbed in the stomach and duodenum. Tissue uptake occurs via sodium iodide symporters with main organs in descending order being thyroid, ovaries, uterine endometrium, stomach and breast

tissue (Venturi *et al.*, 2000; Mahapatra and Chandra, 2017). In adults, the mean daily turnover of iodine by the thyroid is approximately 60–95 µg. In the thyroid gland, iodide is vital for the enzymatic action of thyroid peroxidase and iodination of thyroglobulin, which are essential steps in thyroid hormone synthesis and release. Under normal circumstances, iodine is cleared from the circulation by the kidneys in approximately 10 h (Chung, 2014).

Daily iodine requirement in a normal adult in the reproductive age group is approximately 150 µg per day, with a higher requirement in pregnancy and breastfeeding (200–250 µg and 200–290 µg, respectively) (Harding *et al.*, 2017). The tolerable upper-level threshold without notable adverse effects is 1100 µg/day (Alexander *et al.*, 2017). Median urine iodine concentrations have been widely used as a biomarker of population iodine intake, with levels >300 µg/l considered excessive in adults and >500 µg/l considered excessive in pregnant women (Leung and Braverman, 2014).

Iodine is listed among the micronutrients required for normal female fertility (Buhling and Grajecki, 2013). Severe iodine deficiency can lead to reduced thyroid hormone production in pregnancy. This can have adverse consequences even with milder abnormalities such as subclinical hypothyroidism. Untreated mild elevation of thyroid-stimulating hormone (TSH) in early pregnancy has been found to be associated with increased risk of miscarriages and

adverse perinatal outcome (van den Boogaard et al., 2011; Schneuer et al., 2012).

Maternal iodine also plays a significant role in neurological development of the fetus. It is critical to the synthesis and secretion of the prohormone, thyroxine (T4) and the active hormone triiodothyronine (T3) in the fetus and mother. Maternal iodine deficiency causes increased conversion of T4 to T3, resulting in low maternal T4 levels but a euthyroid state (Greer et al., 1968). As T4 is essential for fetal neurological development, low maternal T4 levels can result in neurocognitive sequelae. In particular, as the fetus is entirely dependent on maternal T4 in early pregnancy, iodine deficiency in the first trimester is an especially vulnerable time (Contempré et al., 1993; Burrow et al., 1994; Calvo et al., 2002). Before successful implementation of iodine fortification, endemic cretinism (defined as goitre with severe irreversible mental and physical retardation) was prevalent in severely iodine deficient populations (Kevany et al., 1969; Pharoah et al., 1971). While severe *in utero* hypothyroidism and cretinism are now rare in developed countries, milder degrees of maternal iodine deficiency result in subtle changes in cognition, with a difference of between 10 and 15 intelligence quotient (IQ) points compared to iodine-sufficient populations (Alexander et al., 2017; Velasco et al., 2018). Indeed, iodine deficiency is considered one of the most common preventable causes of brain damage.

Table 1 summarizes the human studies assessing the maternal and fetal impact of iodine deficiency and supplementation during pregnancy. The early trials showed profound benefits of iodine supplementation (Kevany et al., 1969; Pharoah et al., 1971; Cao et al., 1994) and popularized widespread iodine supplementation programs throughout the world. Later studies suggested that there could be less evident, but still significant, neurocognitive deficits associated with mild iodine deficiency (Bath et al., 2013; Hynes et al., 2013; Abel et al., 2017). There were also some studies suggesting association of preterm birth and low birth weight with mild iodine deficiency (Charoenratana et al., 2016).

The outcome of supplementation in population with mild deficiency has been variable in different studies. Whilst some studies showed definite improvement in full scale IQ and psychomotor scores of the offspring (O'Donnell et al., 2002; Moleti et al., 2016), a recent randomized control trial showed no difference between IQ of children at 5–6 years whether or not the mothers received supplements during pregnancy (Gowachirapant et al., 2017). Systematic reviews assessing impact of gestational iodine supplementation on maternal thyroid function and the neurodevelopment and growth of the offspring again showed inconsistent and modest benefits (Zhou et al., 2013; Taylor et al., 2014).

Furthermore, a few studies raised concern of potential harmful effects from an iodine excess. More than adequate iodine intake was associated with maternal subclinical hypothyroidism (Shi et al., 2015), increased thyroid autoimmunity (Pedersen et al., 2011) and preterm births (Purdue-Smithe et al., 2019). Iodine excess through prenatal vitamins were also found to have negative effects on the offspring's neurodevelopment (Rebagliato et al., 2013), thyroid development (Thomas Jde and Collett-Solberg, 2009) or thyroid function (Connelly et al., 2012).

Iodine excess and its deleterious effects can also occur during pregnancy through dietary sources (Nishiyama et al., 2004), medications affecting iodine metabolism (Lomenick et al., 2004) or preconceptional

hysterosalpingography (HSG) using iodinated contrast (Mekaru et al., 2008; Kaneshige et al., 2015; Satoh et al., 2015; So et al., 2017). The studies and case reports showing impact of iodine excess in pregnancy are summarized in Table II.

Indeed, a U-shaped relationship of pregnancy outcomes with iodine levels has been described (Purdue-Smithe et al., 2019). The maternal and fetal outcome seems best at a relatively narrow range with both deficiency and excess having undesirable consequences.

Unexplained infertility—an enigma

Unexplained infertility (UI) is defined as the lack of conception in a couple after one year of regular unprotected sex and the absence of an identifiable cause for infertility in either of the partners (Gelbaya et al., 2014). The prevalence of UI varies, with different studies, quoting prevalence rates between 5% and 30% (Adamson and Baker, 2003; Isaksson and Tiitinen, 2004). The diagnosis of UI remains controversial because some argue these are missed cases of endometriosis, premature ovarian aging, tubal problems or immunological infertility (Siristatidis and Bhattacharya, 2007). Thus, UI probably reflects a range of pathologies, including conditions that have not been diagnosed but may well be contributing to the infertility.

UI is not an absolute condition, but rather a relative inability to conceive. Many of these couples conceive without treatment and expectant management is often recommended for younger women (Isaksson and Tiitinen, 2004). The rate of spontaneous conception after 1 year of UI is encouraging with 50% conceiving within the next 12 months and a further 12% in the following year (Gelbaya et al., 2014). IUI and IVF are sometimes offered based on clinical judgment, with variable success rate of 15–30% and 30–60%, respectively (Reindollar et al., 2010; Farquhar et al., 2018). The benefit of assisted reproductive technologies over the 'wait and watch' approach is debatable and the success rates are determined by various factors such as the duration of UI, age of patient, number of IUI cycles and use of additional fertility medications such as clomiphene or FSH (Adamson and Baker, 2003; Brandes et al., 2010; Reindollar et al., 2010; Farquhar et al., 2018).

The increased risk of multiple pregnancies and concern of long-term metabolic complications in the offspring highlight the importance of judicious use of IVF and opting for more conservative approaches (Mol et al., 2018). These other treatment modalities are cheaper and promote spontaneous conception or better conception rate following IUI, by favoring implantation. Since the 1950s there have been reports of increased fertility following HSG with Lipiodol, an oil-soluble contrast media. Further studies in the last two decades reinforced these early findings (Johnson et al., 2004, 2007; Johnson, 2014). A recent large randomized study has confirmed these studies and Lipiodol was found to increase fertility rates in UI compared to a water-soluble contrast media (WSCM) (39.7% vs 29.1% over 6 months) (Dreyer et al., 2017; van Rijswijk et al., 2018). Other than being a poppy seed oil-based product, Lipiodol has a number of other characteristics including being relatively viscous, non-ionic and containing more iodine than most other contrast media (480 mg/ml). Individual WSCM used for HSG have physical properties that vary substantively to one another with

Table 1 Prior publications on iodine deficiency and supplementation in pregnancy.

I. Older independent studies assessing impact of iodine supplementation in severely iodine deficient population		
Publication and author	Study setting	Relevant outcome of the study
Kevany et al. (1969)	Quasi RCT using iodized oil (2 ml) or non-iodized poppy seed oil in alternate families in Ecuador and Peru, both severely iodine deficient regions. n = 3183, included 747 women of childbearing age	1. Reduction in the incidence of goitre. 2. Cretinism not seen in the progeny of the population injected with iodized oil, but reported in the control group. 3. In a subgroup analysis comparing women with normal (n = 28) or low (n = 44) iodine excretion, IQ scores were higher and psychological age retardation lower in the group with higher iodine excretion ($P = 0.002$ and $P < 0.0001$, respectively).
Pharoah et al. (1971)	Double blind RCT in the highlands of Papua New Guinea with severe iodine deficiency (1966–1972) n = ~16 500, 4 ml iodized oil in cases and saline in controls	1. Prevention of nervous endemic cretinism in the iodized oil group. 2. Significant difference in 15 years cumulative survival rate. 3. Improved measures of motor and intellectual function in the children born to mothers who received iodine supplementation.
Cao et al. (1994)	Longitudinal study in severely iodine-deficient Xinjiang region of China. Iodine was administered to groups of children from birth to 3 years of age (n = 689) and women at each trimester of pregnancy (n = 295). Treated children and the babies born to the treated women were followed for 2 years.	1. 2% prevalence of moderate or severe neurological abnormalities if gestational iodine was supplemented before third trimester vs 9% if supplemented in third trimester or as a child ($P = 0.008$). 2. The prevalence of microcephaly decreased from 27% in the untreated children to 11% in the treated children ($P = 0.006$), and the mean developmental quotient at 2 years of age increased (90 ± 14 vs 75 ± 18 in the untreated children; $P < 0.001$).
2. Later studies, in mildly iodine deficient population		
2a. Independent studies assessing impact of iodine deficiency during pregnancy on mother and offspring		
Charoenratana et al. (2016)	Pregnant women without thyroid disease and iodine supplementation were recruited in each trimester and followed up for pregnancy outcome 171 iodine deficient ($\text{UIC} < 150 \mu\text{g/l}$) and 219 iodine sufficient women analyzed for pregnancy outcome	Rates of preterm birth and low birthweight were significantly higher in the insufficiency group, 17.5% vs 10.0% ($P = 0.031$) and 19.9% vs 12.3% ($P = 0.042$), respectively. Iodine status was an independent risk of preterm birth and low birthweight.
Bath et al. (2013) Analysis of mother–child pairs from Avon Longitudinal study of parents and children (ALSPAC)	First trimester urine iodine–creatinine ratio of mother was measured and child's IQ was checked at 8 years along and reading ability at 9 years.	After adjusting for confounders, children of women with iodine/creatinine ratio $< 150 \mu\text{g/g}$ were more likely to have scores in the lower quartile for verbal IQ, reading accuracy and reading comprehension than for those with mothers with ratios $> 150 \mu\text{g/g}$.
Hynes et al. (2013)	9-year follow up of gestational iodine cohort. Pregnancy occurred during a period of mild iodine deficiency in population and children grew up in an iodine-replete environment.	Children whose mothers had $\text{UIC} < 150 \mu\text{g/l}$ had a reduction of 10% in spelling, 7.6% in grammar and 5.7% in English literacy performance compared to iodine sufficient mother's children.
Abel et al. (2017)	Population-based prospective observational study (n = 33 047 mother–child pairs) in Norway	Low maternal iodine intake ($< 160 \mu\text{g/day}$) was associated with child language delay ($P = 0.024$), externalizing and internalizing behavioral problems ($P < 0.001$) and fine motor skills ($P = 0.002$).
2b. Independent studies assessing impact of iodine supplementation during pregnancy in population with mild iodine deficiency		
O'Donnell et al. (2002)	Growth and development of children whose mothers received iodine during pregnancy (n = 207). The age of children assessed ranged from 4 to 7.3 years.	Better head circumference and psychomotor scores in school age children if iodine supplementation started in mothers in the first two trimesters compared to later pregnancy or direct administration to the child after birth.
Moleti et al. (2016)	Pilot prospective observational study 4 study groups of 15 mother–child pairs (iodine (I), no iodine (no-I), iodine + LT4 (I + T4) and no iodine + LT4 (no-I + T4))	Children of I and I + T4 mothers had similar verbal, performance, and FSIQs, which were 14, 10 and 13 points higher, respectively, than children born to no-I and no-I + T4 mothers. Neuro-intellectual outcomes in children appear to be more dependent on their mothers' nutritional iodine status than on maternal thyroid function.
Gowachirapant et al. (2017) MITCH study (Maternal Iodine Supplementation and its	Randomized-placebo control trial (n = 832) at two sites (Bangalore, India and Bangkok, Thailand) Cases received $200 \mu\text{g/day}$ iodine orally and controls received placebo from ~10 weeks to until delivery.	Mean WPPSI score for verbal and performance IQ was similar with no statistically significant difference. Similarly the overall executive function score using BRIEF-P was also similar. The conclusion was that daily iodine supplementation in mildly

(continued)

Table I Continued

I. Older independent studies assessing impact of iodine supplementation in severely iodine deficient population		
Publication and author	Study setting	Relevant outcome of the study
effects on Thyroid function and CHild development)	313 children (159 from iodine group and 156 from placebo group) were analyzed for verbal IQ and performance IQ using WPPSI-III and overall executive function using BRIEF-P	iodine deficient pregnant women had no effect on child neuro-development at 5–6 years.
3. Systematic reviews assessing impact of gestational iodine supplementation		
Zhou et al. (2013)	Systematic review to assess the benefits and safety of gestational and peri-conceptual iodine to women on growth and development of children. Secondary outcomes were pregnancy outcome and thyroid function. Eight trials met inclusion criteria, only two studies looked at the main outcomes.	1. Effects of iodine supplementation on the thyroid function of mothers and their children were inconsistent. 2. Lack of high quality RCTs to assess growth and development outcome. Growth and development outcome not recorded in 6/8 studies. The only two trials which assessed growth and developmental outcome were conducted in areas of severe iodine deficiency showed clear benefits.
Taylor et al. (2014)	Meta-analysis of nine RCT and eight observational studies on gestational iodine supplementation.	Gestational iodine supplementation reduced maternal thyroid volume and serum thyroglobulin and in some studies prevented a rise in serum TSH. Though the observational studies showed increased frequency of thyroid dysfunction, the interventional trials did not confirm this. A pooled analysis of two RCTs which measured cognitive function in school age children showed modest benefits.

BRIEF-P, Behavior Rating Inventory of Executive Function-Preschool version; FSIQ, full scale intelligence quotient; IQ, intelligence quotient; LT4, levothyroxine; RCT, randomized controlled trial; TSH, thyroid-stimulating hormone; UIC, urine iodine concentration; WPPSI, Wechsler Preschool and Primary Scale of Intelligence.

respect to ionicity, viscosity, hyperosmolarity and iodine content. The iodine content, however, has always been less than Lipiodol with concentrations between 250 and 380 mg/ml (Rasmussen et al., 1991; Fang et al., 2018). Lipiodol also has a much longer half-life if retained in the body (50 days vs 2–3 h for WSCM) which can lead to prolonged iodine exposure (Brown et al., 1949; Miyamoto et al., 1995). The underlying mechanism(s) by which Lipiodol improves conception rates remain unclear but are likely multifactorial. These include a flushing effect of removing debris and obstructions from the fallopian tubes (van Welie et al., 2019), an immunobiological peritoneal bathing effect (Izumi et al., 2017) and an immunobiological uterine bathing effect of the Lipiodol on the endometrium favoring implantation (Johnson et al., 2019). However, the uniquely high iodine concentration and long half-life of Lipiodol warrants consideration of iodine as a potential factor improving fertility.

Could iodine deficiency explain some cases of unexplained infertility?

The term 'iodine deficiency disorders' (IDD) comprises a spectrum ranging from subclinical hypothyroidism to endemic cretinism. Reduced fertility and impaired fetal development are listed among the many manifestations of iodine deficiency and hence are part of the IDD spectrum (Dunn and Delange, 2001). It is well known that deficiency of this trace element is associated with abortions, still births and congenital anomalies (Semba and Delange, 2008). More recently, Mills et al. (2018) conducted a study in over 500 women in the USA

and found that those with lower urinary iodide levels had a 46% reduction in fertility. Moreover, women with low iodine levels also took longer to conceive, with 28% of the iodine deficient group failing to conceive at 12 months compared to only 12.5% in the iodine sufficient group. This suggests that iodine deficiency may contribute to a proportion of UI in developed countries (Mills et al., 2018). Another study in West Africa showed that women with iodine deficiency have twice the risk of reproductive failure and again, the risk of reproductive failure being directly proportional to the severity of iodine deficiency (Dillon and Milliez, 2000). While a recent prospective cohort study did not find an association between iodine deficiency and pregnancy losses (Mills et al., 2019), current data suggests that iodine plays an important role in conception and ongoing pregnancy.

Insights from animal studies

There has been little research done in humans, but research in animal models studying the effect of iodine on uterus and ovaries has provided insight into the relationship between iodine and fertility.

Iodine-uterine effects

Cows with UI showed improved fertility when treated with uterine instillation of Lugol's iodine. The authors postulated that infertility was secondary to subclinical endometritis and improvement could be due to potent bactericidal action of iodine to restore damaged endometrium. Other mechanisms suggested were changes in the uterine pH and improved uterine vascularity (Ahmed and Elsheikh, 2013, 2014).

Table II Prior publications on iodine excess in pregnancy.

I. Effects on maternal thyroid function			
Publication year and author	Source of iodine excess	Study methodology/ characteristics	Relevant outcome
Kaneshige <i>et al.</i> (2015)	Hysterosalpingogram with Lipiodol dye (Lipiodol HSG)	Prospective cohort study-urinary iodine levels and TSH of 22 women who underwent Lipiodol HSG	Increased incidence of transient SCH following Lipiodol HSG. Biochemical hypothyroidism with rise in TSH corresponding to elevated iodine levels from 4 to 24 weeks following Lipiodol HSG.
Mekaru <i>et al.</i> (2008)	Lipiodol HSG	Retrospective study-TFT analysis of 214 women who underwent Lipiodol HSG	14 women (6.5%) developed hypothyroidism. This included 10/28 (35.5%) in the group with baseline subclinical hypothyroidism and 4/180(2.2%) among those who were baseline euthyroid. This suggested higher incidence of hypothyroidism in those with underlying SCH.
Soet <i>et al.</i> (2017)	OSCM or WSCM HSG	Retrospective study-TFT analysis of 164 women who underwent HSG with OSCM and 94 women who underwent HSG with WSCM	22.6% of women in OSCM group developed subclinical hypothyroidism whereas 9.5% in the WSCM group developed SCH. The increase in TSH value post OSCM HSG was statistically significant ($P < 0.05$).
Shi <i>et al.</i> (2015)	Dietary iodine	7190 pregnant women checked for UIC, TFT, thyroid antibodies and Tg at 4–8 weeks gestation	More-than-adequate iodine intake (UIC 250–499 µg/l) and excessive iodine intake (UIC ≥ 500 µg/l) were associated with a 1.72-fold and a 2.17-fold increased risk of subclinical hypothyroidism, respectively. Meanwhile, excessive iodine intake was associated with a 2.85-fold increased risk of isolated hypothyroxinemia.
Pedersen <i>et al.</i> (2011)	Introduction of population based iodine supplementation of bread and household salt aiming to increase iodine intake by an average 50 µg/day	Cross-sectional population studies in Denmark in 1997–1998 ($n = 4649$) and 2004–2005 ($n = 3570$). The second cohort was after 4–5 years of introduction of mandatory iodine supplementation. (Age group 15–65 years, included reproductive age group women)	In all sex and age groups, the prevalence rate of TPO-Ab and/or Tg-Ab increased significantly. The prevalence rate of Tg-Ab increased significantly in women aged 18–45.
Rebagliato <i>et al.</i> (2013)	Iodine supplements	$n = 1519$, children assessed with Bayley scales of infant development	Maternal iodine consumption of 150 µg/day or more of iodine from supplements was related to 1.5-fold increase in the odds of a psychomotor score less than 85 and 1.7-fold increase in the odds of a mental score less than 85.
2. Effects on pregnancy outcome			
Purdue-Smithe <i>et al.</i> (2019)	Dietary iodine	Prospective, population-based, nested case-control study from Finland (2012–2013). Serum iodide, Tg and TSH measurement at 10–14 weeks gestation. ($n = 208$)	Each log-unit increase in serum iodide was associated with higher odds of preterm birth (adjusted OR = 1.19, 95% CI = 1.02–1.40). But no association between iodine status and small-for-gestation.
3. Effects on neonatal thyroid function			
Satoh <i>et al.</i> (2015)	Preconception HSG	Retrospective study-212 new-borns conceived following Lipiodol HSG in mothers assessed for congenital hypothyroidism (CH)	Five out of 212 had new-born TSH abnormalities with two having permanent hypothyroidism and three with hyperthyrotropinemia. This is a rate of ~ 1 in 100 as against a background

(continued)

Table II Continued

I. Effects on maternal thyroid function

Publication year and author	Source of iodine excess	Study methodology/ characteristics	Relevant outcome
van Welie et al. (2020)	Preconception HSG	Retrospective TSH analysis of babies conceived after Lipiodol HSG, n = 140 (76 OSCM and 64 WSCM)	incidence of one in 2000 for CH in Japan. No abnormal new-born screen for hypothyroidism (T4 based screening)
Lomenick et al. (2004)	Amiodarone in pregnancy (75 000 µg iodine/tablet)	Analysis of 69 case reports of amiodarone use in pregnancy	23% infants (16/69) developed hypothyroidism and two developed hyperthyroidism. 56% of hypothyroid infants were exposed to amiodarone in the third trimester.
Thomas Jde and Collett-Solberg (2009)	Prenatal vitamins with high iodine (error in formulation- 400 times the recommended daily dietary intake)	Medical record review of children presenting with congenital goitre in 2003-pubmed search of publications	Prenatal vitamin containing excess iodine resulted in eight cases of congenital goitre, with three of them with hypothyroidism needing thyroxine. Three babies (two hypothyroid and one euthyroid) had thyroid scintigraphy similar to dysmorphogenesis.
Nishiyama et al. (2004)	Maternal dietary iodine	Analysis of babies with congenital new-born thyroid screen positivity	Fifteen had hyperthyrotropinemia secondary to high iodine intake in mothers (480–3180 µg/day). Twelve of these babies required thyroxine.
Connelly et al. (2012)	Prenatal vitamins containing high iodine (12 500 µg/day of iodine)	Case report	Three infants with CH detected in new-born screening were associated with excess maternal iodine intake, high iodine level in baby's blood and urine.

OR, odds ratio; OSCM, oil-soluble contrast medium; SCH, subclinical hypothyroidism; TFT, thyroid function test; Tg-Ab, thyroglobulin antibody; TPO-Ab, thyroid peroxidase antibody; UIC, urine iodine concentration; WSCM, water-soluble contrast medium.

Lipiodol was studied in rats to understand its effect in the uterus. Rats demonstrated alteration in the endometrial dendritic cell phenotype after Lipiodol instillation. Dendritic cells are important antigen presenting cells and may regulate establishment and maintenance of implanted embryo, which is foreign to the endometrium (Johnson et al., 2005). With each ml of Lipiodol having 480 mg of iodine, it is possible that iodine is the component in Lipiodol responsible for this immunological change in the uterine endometrium, improving implantation of the embryo. On the other hand, a large volume of iodine (50 ml) instilled into the uteri of mares resulted in severe edema and hemorrhage in the lamina propria with vacuolization, necrosis and blood vessel changes (van Dyk and Lange, 1986). This study suggests that large doses of iodine can be toxic while smaller doses such as that in the rat study may be beneficial in inducing a favorable uterine environment for normal reproduction.

Iodine-ovarian effects

Iodine is essential for normal thyroid hormone synthesis and release and thereby indirectly promotes ovulation. Normal TSH promotes follicular growth in oocytes. TSH acts on the FSH receptors due to the structural similarity and enhances FSH induced pre antral follicular growth (Kobayashi et al., 2009).

In addition, iodine has direct action on the ovaries. Second only to the thyroid gland, ovaries have significant expression of the sodium-iodine symporter gene and this leads to iodine accumulation in ovaries after a large dose of iodine. The reason for the high ovarian iodine uptake remains largely unknown. However, studies done to understand the effect of radioactive iodine treatment on ovaries demonstrated that small and growing follicles take up more iodine and this appears to be crucial for ovarian granulosa cell secretory activities (Slebodziński, 2005). Iodine first accumulates in the walls of large Graafian follicles with maximal uptake by 4 h, followed by a shift to the follicular fluid. Estrogen can modify the iodine uptake by ovaries. Estradiol increases proliferation, but down-regulates the sodium-iodine symporter gene expression (Furlanetto et al., 1999).

Iodine deficiency, when artificially created in cows, resulted in anovulatory cycles. In contrast, pregnancy rates improved after adding iodine to their feeds, suggesting a causal-effect relationship between iodine and ovulation (Hidioglou, 1979). Again, the optimal level of iodine is critical and excess iodine can have deleterious effects on ovaries as shown by Mahapatra and Chandra (2017) and Mahapatra et al. (2017) in murine studies. The iodine toxicity to ovaries was dose-dependent in their studies and associated with a negative fertility index. While 100-fold elevation of iodine levels produced hypoestrogenemia

in rats, a 500-fold elevation resulted in hyperthyroxinemia and subsequent hyperestrogenemia, both situations negatively affecting fertility (Mahapatra and Chandra, 2017). These animal studies again point to an optimal iodine level necessary for normal ovarian reserve and reproductive function.

Iodine-immunological effects

Successful pregnancy involves a complex interplay between immune cells and cytokines to promote or restrain inflammation at the maternal–fetal interface. An imbalance between Th17 (T helper cell), Treg (regulatory T cell) and NK cells (natural killer cell) can result in unexplained spontaneous recurrent abortions (Zhao *et al.*, 2018). Dysregulated lymphocyte subsets and abnormal expression of cytokines were also found to be associated with recurrent implantation failure in women with chronic endometriosis (Wang *et al.*, 2019). Iodine excess can alter the lymphocyte subset population as demonstrated by murine studies (Johnson *et al.*, 2005; Yang *et al.*, 2014; Saha *et al.*, 2019). Murine studies examining the pathogenesis of autoimmune thyroiditis after an iodine load revealed that excess iodine upregulated Th17 cells, promoting inflammation. In addition, there was suppression of Treg cells (Yang *et al.*, 2014). These studies suggest that iodine alters immunological milieu, potentially playing a role in embryo implantation. It is possible this could be detrimental to pregnancy length, with one population trial showing that each log-unit increase in serum iodide was associated with higher odds of preterm birth (Purdue-Smithe *et al.*, 2019). Our literature review did not find any evidence to suggest increased or recurrent pregnancy losses with iodine excess. Similarly, there was no evidence that iodine deficiency seen at the levels in the current developed world resulted in increased pregnancy loss (Mills *et al.*, 2019).

Ideal therapeutic iodine supplementation in UI

Lipiodol HSG has been shown to improve fertility in women with endometriosis and UI (Johnson *et al.*, 2004; Mohiyiddeen *et al.*, 2015; Dreyer *et al.*, 2017; van Rijswijk *et al.*, 2018).

However, a study in a small group of 22 women by Kaneshige *et al.* (2015) raised safety concerns, with 100-fold elevation of iodine levels in women undergoing Lipiodol HSG procedure. With Lipiodol having a long half-life (50 days) and assuming a conservative 2 ml of Lipiodol is retained following an HSG, about 480 mg of iodine is released in the initial 50 days. This is approximately 10 000 µg/day, which is more than 50 times the recommended daily allowance. Even after 5 half-lives or 250 days, about 600 µg/day of iodine is released, which is still 3-fold the normal requirement. Excess iodine load can cause transient hypothyroidism by the Wolff–Chaikoff effect (Leung and Braverman, 2014). In certain situations, such as autoimmune thyroiditis and in the fetus and neonate, the effect may be more severe and persistent resulting in prolonged hypothyroidism.

Indeed, an increased incidence of transient subclinical hypothyroidism in women undergoing Lipiodol HSG has been shown (Mekaru *et al.*, 2008; Kaneshige *et al.*, 2015; So *et al.*, 2017). Suppression of thyroid function was more enhanced in those with

baseline subclinical hypothyroidism, with more than a third developing overt hypothyroidism (Mekaru *et al.*, 2008). In addition, thyroid suppression following Lipiodol (480 mg iodine) lasted longer compared to that caused by water-soluble contrast (Isovist, 300 mg iodine) (So *et al.*, 2017). Importantly, these studies were in Japanese populations who generally had sufficient or excess iodine at baseline due to seaweed consumption and extrapolation to other populations may not be possible. In addition, these studies did not directly compare the iodine levels to the thyroid function and had methodological issues including variable timing of thyroid function assessment.

Excess iodine during pregnancy can also potentially affect the fetal thyroid gland development and neonatal thyroid function. There have been multiple case reports of amiodarone therapy during pregnancy causing newborn hypothyroidism (Laurent *et al.*, 1987; Bretremieux *et al.*, 1988; Aguilar *et al.*, 1992; Bartalena *et al.*, 2001). The thyroid dysfunction was transient with the neonates requiring only short term thyroid hormone replacement, suggesting the underlying etiology was fetal iodine exposure and a prolonged Wolff–Chaikoff effect causing suppression of fetal thyroid hormone release (Lomenick *et al.*, 2004). Transient TSH abnormalities and permanent hypothyroidism were similarly observed in babies conceived in the immediate cycles following Lipiodol HSG in a study on 212 neonates conceived within 6 months of Lipiodol HSG in Japan (Satoh *et al.*, 2015). This, however, was not replicated in a later study on a Caucasian population (van Welie *et al.*, 2020) which found no increase in hypothyroidism for babies conceived following Lipiodol HSG. The later study was a *post hoc* analysis in a Dutch population and used a screening program with T4 followed by TSH, possibly missing cases of transient thyrotropinemia.

This brings us to the possibilities of alternative methods of Lipiodol or iodine administration with similar fertility advantage, but better safety profile. Whether iodine given either by a subcutaneous or intramuscular route improves fertility to the same extent as Lipiodol HSGs remains unclear. Lipiodol given as single oral dose of three capsules (570 mg of iodine) vs a single intramuscular dose (1 ml of Lipiodol–480 mg of iodine) produced similar iodine profile in a case–control study with no clinical or laboratory adverse effects (Leverge *et al.*, 2003). Subcutaneous single dose of Lipiodol in iodine-deficient sheep resulted in 100% pregnancy rates vs 37% among the controls (Ferri *et al.*, 2003). Oral and intramuscular iodized oil had similar effectiveness in prevention of thyroid disorders in Zaire (Phillips *et al.*, 1988).

In conclusion, more studies are warranted to understand the role of iodine and Lipiodol in UI. Lipiodol hysterosalpingography has proven beneficial in UI, however the safety aspects of chronic iodine excess need further study. It is possible that higher iodine levels improve conception and this will need to be balanced against the potential for maternal and offspring morbidity. The safe and efficacious dose in UI, iodine preparation and route of administration are also areas that require further research.

Data availability

No new data were generated or analyzed in support of this research.

Authors' roles

D.M.M. and P.L.H. conceptualized the paper, D.M.M. wrote the manuscript, P.L.H., N.P.J., R.G.S., S.O.S., and J.M.P. revised critically and improvised the intellectual content and all authors approved the final version of the manuscript.

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Conflict of interest

Authors have no conflict of interest to declare related to this manuscript. However, 'Lipiodol' is mentioned several times in the manuscript. N.P.J. is involved in research with the University of Auckland and the University of Adelaide that is funded by Guerbet, the manufacturer of Lipiodol; N.P.J. has undertaken paid consultancies for Guerbet. D.M.M. and P.L.H. are involved with University of Auckland research on Lipiodol safety through an unrestricted independent grant to the Liggins institute, Auckland by Guerbet. P.L.H. has also received fees for speaking in two webinars sponsored by Guerbet. R.G.S. and J.M.P. have been paid for presenting and being an advisory board member by Guerbet. R.G.S., J.M.P. and N.P.J. undertake Lipiodol HSGs as a part of their profession.

References

- Abel MH, Caspersen IH, Meltzer HM, Haugen M, Brandlistuen RE, Aase H, Alexander J, Torheim LE, Brantsæter AL. Suboptimal maternal iodine intake is associated with impaired child neurodevelopment at 3 years of age in the norwegian mother and child cohort study. *J Nutr* 2017;**147**:1314–1324.
- Adamson GD, Baker VL. Subfertility: causes, treatment and outcome. *Best Pract Res Clin Obstet Gynaecol* 2003;**17**:169–185.
- Aguilar DM, Jáen AF, Gavilán VI, Merino LF. Neonatal Hypothyroidism after Amiodarone Therapy during Pregnancy. *Anales de Medicina Interna (Madrid, Spain: 1984)*. 1992, 358.
- Ahmed FO, Elsheikh AS. Treatment of repeat breeding in dairy cows with Lugol's Iodine. *IOSR-JAVS* 2014;**7**:22–26.
- Ahmed FO, Elsheikh ASJL. Intrauterine infusion of lugol's iodine improves the reproductive traits of postpartum infected dairy cows. *IOSR-JAVS* 2013;**5**:89–94.
- Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid* 2017;**27**:315–389.
- Bartalena L, Bogazzi F, Braverman LE, Martino E. Effects of amiodarone administration during pregnancy on neonatal thyroid function and subsequent neurodevelopment. *J Endocrinol Invest* 2001;**24**:116–130.
- Bath SC, Steer CD, Golding J, Emmett P, Rayman MP. Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). *Lancet* 2013;**382**:331–337.
- Brandes M, Hamilton CJ, de Bruin JP, Nelen WL, Kremer JA. The relative contribution of IVF to the total ongoing pregnancy rate in a subfertile cohort. *Hum Reprod* 2010;**25**:118–126.
- Bretremieux P, Laurent M, Almange C, Lefrançois C. [Hypothyroidism following maternal treatment with amiodarone]. *J Gynecol Obstet Biol Reprod* 1988;**17**:398.
- Brown WE, Jennings AF, Bradbury JT. The absorption of radiopaque substances used in hysterosalpingography; a comparative study of various aqueous and oily media. *Am J Obstet Gynecol* 1949;**58**:1041–1053.
- Buhling KJ, Grajecki D. The effect of micronutrient supplements on female fertility. *Curr Opin Obstet Gynecol* 2013;**25**:173–180.
- Burrow GN, Fisher DA, Larsen PR. Maternal and fetal thyroid function. *N Engl J Med* 1994;**331**:1072–1078.
- Calvo RM, Jauniaux E, Gulbis B, Asunción M, Gervy C, Contempré B, Morreale de Escobar G. Fetal tissues are exposed to biologically relevant free thyroxine concentrations during early phases of development. *J Clin Endocrinol Metab* 2002;**87**:1768–1777.
- Cao XY, Jiang XM, Dou ZH, Rakeman MA, Zhang ML, O'Donnell K, Ma T, Amette K, DeLong N, DeLong GR. Timing of vulnerability of the brain to iodine deficiency in endemic cretinism. *N Engl J Med* 1994;**331**:1739–1744.
- Charoenratana C, Leelapat P, Traisrisilp K, Tongsong T. Maternal iodine insufficiency and adverse pregnancy outcomes. *Matern Child Nutr* 2016;**12**:680–687.
- Chung HR. Iodine and thyroid function. *Ann Pediatr Endocrinol Metab* 2014;**19**:8–12.
- Connelly KJ, Boston BA, Pearce EN, Sesser D, Snyder D, Braverman LE, Pino S, LaFranchi SH. Congenital hypothyroidism caused by excess prenatal maternal iodine ingestion. *J Pediatr* 2012;**161**:760–762.
- Contempré B, Jauniaux E, Calvo R, Jurkovic D, Campbell S, de Escobar GM. Detection of thyroid hormones in human embryonic cavities during the first trimester of pregnancy. *J Clin Endocrinol Metab* 1993;**77**:1719–1722.
- Dillon JC, Milliez J. Reproductive failure in women living in iodine deficient areas of West Africa. *BJOG* 2000;**107**:631–636.
- Dreyer K, van Rijswijk J, Mijatovic V, Goddijn M, Verhoeve HR, van Rooij IAJ, Hoek A, Bourdrez P, Nap AW, Rijnsaardt-Lukassen HGM et al. Oil-based or water-based contrast for hysterosalpingography in infertile women. *N Engl J Med* 2017;**376**:2043–2052.
- Dunn JT, Delange F. Damaged reproduction: the most important consequence of iodine deficiency. *J Clin Endocrinol Metab* 2001;**86**:2360–2363.
- Fang F, Bai Y, Zhang Y, Faramand A. Oil-based versus water-based contrast for hysterosalpingography in infertile women: a systematic review and meta-analysis of randomized controlled trials. *Fertil Steril* 2018;**110**:153–160.e3.
- Farquhar CM, Liu E, Armstrong S, Arroll N, Lensen S, Brown J. Intrauterine insemination with ovarian stimulation versus expectant management for unexplained infertility (TUI): a pragmatic, open-label, randomised, controlled, two-centre trial. *Lancet* 2018;**391**:441–450.

- Ferri N, Ulisse S, Aghini-Lombardi F, Graziano FM, Di Mattia T, Russo FP, Arizzi M, Baldini E, Trimboli P, Attanasio D et al. Iodine supplementation restores fertility of sheep exposed to iodine deficiency. *J Endocrinol Invest* 2003;**26**:1081–1087.
- Furlanetto TW, Nguyen LQ, Jameson JL. Estradiol increases proliferation and down-regulates the sodium/iodide symporter gene in FRTL-5 cells. *Endocrinology* 1999;**140**:5705–5711.
- Gelbaya TA, Potdar N, Jeve YB, Nardo LG. Definition and epidemiology of unexplained infertility. *Obstet Gynecol Surv* 2014;**69**:109–115.
- Gowachirapant S, Jaiswal N, Melse-Boonstra A, Galetti V, Stinca S, Mackenzie I, Thomas S, Thomas T, Winichagoon P, Srinivasan K et al. Effect of iodine supplementation in pregnant women on child neurodevelopment: a randomised, double-blind, placebo-controlled trial. *Lancet Diab Endocrinol* 2017;**5**:853–863.
- Greer MA, Grimm Y, Studer H. Qualitative changes in the secretion of thyroid hormones induced by iodine deficiency. *Endocrinology* 1968;**83**:1193–1198.
- Harding KB, Peña-Rosas JP, Webster AC, Yap CM, Payne BA, Ota E, De-Regil LM. Iodine supplementation for women during the pre-conception, pregnancy and postpartum period. *Cochrane Database Syst Rev* 2017;**3**:CD011761.
- Hidirolglou M. Trace element deficiencies and fertility in ruminants: a review. *J Dairy Sci* 1979;**62**:1195–1206.
- Hynes KL, Otahal P, Hay I, Burgess JR. Mild iodine deficiency during pregnancy is associated with reduced educational outcomes in the offspring: 9-year follow-up of the gestational iodine cohort. *J Clin Endocrinol Metab* 2013;**98**:1954–1962.
- Isaksson R, Tiitinen A. Present concept of unexplained infertility. *Gynecol Endocrinol* 2004;**18**:278–290.
- Izumi G, Koga K, Takamura M, Bo W, Nagai M, Miyashita M, Harada M, Hirata T, Hirota Y, Yoshino O et al. Oil-soluble contrast medium (OSCM) for hysterosalpingography modulates dendritic cell and regulatory t cell profiles in the peritoneal cavity: a possible mechanism by which OSCM enhances fertility. *J Immunol* 2017;**198**:4277–4284.
- Johnson N, Baidya S, Jessup S, Print C, Muthukaruppan A, Chamley L, Hadden W, Hull M, Mehta S, Shelling AJF. Randomised trial of lipiodol uterine bathing effect (LUBE) in women with endometriosis-related infertility. *FandR* 2019;**01**:57–64.
- Johnson NP, Bhattu S, Wagner A, Blake DA, Chamley LW. Lipiodol alters murine uterine dendritic cell populations: a potential mechanism for the fertility-enhancing effect of lipiodol. *Fertil Steril* 2005;**83**:1814–1821.
- Johnson NP, Farquhar CM, Hadden WE, Suckling J, Yu Y, Sadler L. The FLUSH trial—flushing with lipiodol for unexplained (and endometriosis-related) subfertility by hysterosalpingography: a randomized trial. *Hum Reprod* 2004;**19**:2043–2051.
- Johnson NP, Kwok R, Stewart AW, Saththianathan M, Hadden WE, Chamley LW. Lipiodol fertility enhancement: two-year follow-up of a randomized trial suggests a transient benefit in endometriosis, but a sustained benefit in unexplained infertility. *Hum Reprod* 2007;**22**:2857–2862.
- Johnson NP. Review of lipiodol treatment for infertility—an innovative treatment for endometriosis-related infertility? *Aust N Z J Obstet Gynaecol* 2014;**54**:9–12.
- Kaneshige T, Arata N, Harada S, Ohashi T, Sato S, Umehara N, Saito T, Saito H, Murashima A, Sago H. Changes in serum iodine concentration, urinary iodine excretion and thyroid function after hysterosalpingography using an oil-soluble iodinated contrast medium (lipiodol). *J Clin Endocrinol Metab* 2015;**100**:E469–E472.
- Kevany J, Fierro-Benitez R, Pretell EA, Stanbury JB. Prophylaxis and treatment of endemic goiter with iodized oil in rural Ecuador and Peru. *Am J Clin Nutr* 1969;**22**:1597–1607.
- Kobayashi N, Orisaka M, Cao M, Kotsuji F, Leader A, Sakuragi N, Tsang BK. Growth differentiation factor-9 mediates follicle-stimulating hormone-thyroid hormone interaction in the regulation of rat preantral follicular development. *Endocrinology* 2009;**150**:5566–5574.
- Laurent M, Betremieux P, Biron Y, Lebelloc A. Neonatal hypothyroidism after treatment by amiodarone during pregnancy. *Am J Cardiol* 1987;**60**:942.
- Leung AM, Braverman LE. Consequences of excess iodine. *Nat Rev Endocrinol* 2014;**10**:136–142.
- Leverge R, Bergmann JF, Simoneau G, Tillet Y, Bonnemain B. Bioavailability of oral vs intramuscular iodinated oil (Lipiodol UF) in healthy subjects. *J Endocrinol Invest* 2003;**26**:20–26.
- Lomenick JP, Jackson WA, Backeljauw PF. Amiodarone-induced neonatal hypothyroidism: a unique form of transient early-onset hypothyroidism. *J Perinatol* 2004;**24**:397–399.
- Mahapatra D, Chandra AK. Biphasic action of iodine in excess at different doses on ovary in adult rats. *J Trace Elem Med Biol* 2017;**39**:210–220.
- Mahapatra D, Chattopadhyay S, Chandra AK. Iodine in excess: impact on ovarian and uterine histology in adult rats. *Indian J Physiol Pharmacol* 2017;**61**:166–174.
- Mekaru K, Kamiyama S, Masamoto H, Sakumoto K, Aoki Y. Thyroid function after hysterosalpingography using an oil-soluble iodinated contrast medium. *Gynecol Endocrinol* 2008;**24**:498–501.
- Mills JL, Ali M, Buck Louis GM, Kannan K, Weck J, Wan Y, Maisog J, Giannakou A, Sundaram R. Pregnancy loss and iodine status: the LIFE Prospective Cohort Study. *Nutrients* 2019;**11**:534.
- Mills JL, Buck Louis GM, Kannan K, Weck J, Wan Y, Maisog J, Giannakou A, Wu Q, Sundaram R. Delayed conception in women with low-urinary iodine concentrations: a population-based prospective cohort study. *Hum Reprod* 2018;**33**:426–433.
- Miyamoto Y, Tsujimoto T, Iwai K, Ishida K, Uchimoto R, Miyazawa T, Azuma H. Safety and pharmacokinetics of iotrolan in hysterosalpingography. Retention and irritability compared with Lipiodol. *Invest Radiol* 1995;**30**:538–543.
- Mohiyiddeen L, Hardiman A, Fitzgerald C, Hughes E, Mol BW, Johnson N, Watson A. Tubal flushing for subfertility. *Cochrane Database Syst Rev* 2015;**2015**:CD003718.
- Mol BW, Tjon-Kon-Fat R, Kamphuis E, van Wely M. Unexplained infertility: Is it over-diagnosed and over-treated? *Best Pract Res Clin Obstet Gynaecol* 2018;**53**:20–29.
- Moleti M, Trimarchi F, Tortorella G, Candia Longo A, Giorgianni G, Sturniolo G, Alibrandi A, Vermiglio F. Effects of maternal iodine nutrition and thyroid status on cognitive development in offspring: a pilot study. *Thyroid* 2016;**26**:296–305.
- Nishiyama S, Makeda T, Okada T, Nakamura K, Kotani T, Hishinuma A. Transient hypothyroidism or persistent hyperthyrotropinemia in

- neonates born to mothers with excessive iodine intake. *Thyroid* 2004;**14**:1077–1083.
- O'Donnell KJ, Rakeman MA, Zhi-Hong D, Xue-Yi C, Mei ZY, DeLong N, Brenner G, Tai M, Dong W, DeLong GR. Effects of iodine supplementation during pregnancy on child growth and development at school age. *Dev Med Child Neurol* 2002;**44**:76–81.
- Pedersen IB, Knudsen N, Carlé A, Vejbjerg P, Jørgensen T, Perrild H, Ovesen L, Rasmussen LB, Laurberg P. A cautious iodization programme bringing iodine intake to a low recommended level is associated with an increase in the prevalence of thyroid autoantibodies in the population. *Clin Endocrinol* 2011;**75**:120–126.
- Pharoah PO, Butfield IH, Hetzel BS. Neurological damage to the fetus resulting from severe iodine deficiency during pregnancy. *Lancet* 1971;**297**:308–310.
- Phillips DI, Lusty TD, Osmond C, Church D. Iodine supplementation: comparison of oral or intramuscular iodized oil with oral potassium iodide. A controlled trial in Zaire. *Int J Epidemiol* 1988;**17**:142–147.
- Purdue-Smithe AC, Männistö T, Bell GA, Mumford SL, Liu A, Kannan K, Kim U-J, Suvanto E, Surcel H-M, Gissler M et al. The joint role of thyroid function and iodine status on risk of preterm birth and small for gestational age: a population-based nested case-control study of Finnish women. *Nutrients* 2019;**11**:2573.
- Rasmussen F, Lindequist S, Larsen C, Justesen P. Therapeutic effect of hysterosalpingography: oil- versus water-soluble contrast media—a randomized prospective study. *Radiology* 1991;**179**:75–78.
- Rebagliato M, Murcia M, Alvarez-Pedrerol M, Espada M, Fernández-Somoano A, Lertxundi N, Navarrete-Muñoz EM, Forns J, Aranbarri A, Llop S et al. Iodine supplementation during pregnancy and infant neuropsychological development. INMA Mother and Child Cohort Study. *Am J Epidemiol* 2013;**177**:944–953.
- Reindollar RH, Regan MM, Neumann PJ, Levine BS, Thornton KL, Alper MM, Goldman MB. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial. *Fertil Steril* 2010;**94**:888–899.
- Saha A, Mukherjee S, Bhattacharjee A, Sarkar D, Chakraborty A, Banerjee A, Chandra AK. Excess iodine-induced lymphocytic impairment in adult rats. *Toxicol Mech Methods* 2019;**29**:110–118.
- Satoh M, Aso K, Katagiri Y. Thyroid dysfunction in neonates born to mothers who have undergone hysterosalpingography involving an oil-soluble iodinated contrast medium. *Horm Res Paediatr* 2015;**84**:370–375.
- Schneuer FJ, Nassar N, Tasevski V, Morris JM, Roberts CL. Association and predictive accuracy of high TSH serum levels in first trimester and adverse pregnancy outcomes. *J Clin Endocrinol Metab* 2012;**97**:3115–3122.
- Semba RD, Delange F. Iodine deficiency disorders. In: Richard D. Semba, Martin W. Bloem, Peter Piot (eds). *Nutrition and Health in Developing Countries*. Nutrition and Health Series. Humana Press, 2008, 507–529. doi:10.1007/978-1-59745-464-3_17
- Shi X, Han C, Li C, Mao J, Wang W, Xie X, Li C, Xu B, Meng T, Du J et al. Optimal and safe upper limits of iodine intake for early pregnancy in iodine-sufficient regions: a cross-sectional study of 7190 pregnant women in China. *J Clin Endocrinol Metab* 2015;**100**:1630–1638.
- Siristatidis C, Bhattacharya S. Unexplained infertility: does it really exist? *Hum Reprod* 2007;**22**:2084–2087.
- Slebodziński AB. Ovarian iodide uptake and triiodothyronine generation in follicular fluid. The enigma of the thyroid ovary interaction. *Domest Anim Endocrinol* 2005;**29**:97–103.
- So S, Yamaguchi W, Tajima H, Nakayama T, Tamura N, Kanayama N, Tawara F. The effect of oil and water-soluble contrast medium in hysterosalpingography on thyroid function. *Gynecol Endocrinol* 2017;**33**:682–685.
- Taylor PN, Okosieme OE, Dayan CM, Lazarus JH. Therapy of endocrine disease: impact of iodine supplementation in mild-to-moderate iodine deficiency: systematic review and meta-analysis. *Eur J Endocrinol* 2014;**170**:R1–R15.
- Thomas Jde V, Collett-Solberg PF. Perinatal goiter with increased iodine uptake and hypothyroidism due to excess maternal iodine ingestion. *Horm Res Paediatr* 2009;**72**:344–347.
- van den Boogaard E, Vissenberg R, Land JA, van Wely M, van der Post JA, Goddijn M, Bisschop PH. Significance of (sub)clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. *Hum Reprod Update* 2011;**17**:605–619.
- van Dyk E, Lange AL. The detrimental effect of iodine as an intra-uterine instillation in mares. *J S Afr Vet Assoc* 1986;**57**:205–210.
- van Rijswijk J, Pham CT, Dreyer K, Verhoeve HR, Hoek A, de Bruin J-P, Nap AWW, Wang R, Lambalk CB, Hompes PGA et al. Oil-based or water-based contrast for hysterosalpingography in infertile women: a cost-effectiveness analysis of a randomized controlled trial. *Fertil Steril* 2018;**110**:754–760.
- van Welie N, Dreyer K, van Rijswijk J, Verhoeve HR, Goddijn M, Nap AWW, Smeenk MJ, Traas MAF, Rijnsaardt-Lukassen HGM, van Dongen A et al. Treatment effect of oil-based contrast is related to experienced pain at HSG: a post-hoc analysis of the randomised H2Oil study. *Hum Reprod* 2019;**34**:2391–2398.
- van Welie N, Roest I, Portela M, van Rijswijk J, Koks C, Lambalk CB, Dreyer K, Mol BWJ, Finken MJ, Mijatovic V; the H2Oil Study Group. Thyroid function in neonates conceived after hysterosalpingography with iodinated contrast. *Hum Reprod* 2020;**35**:1159–1167.
- Velasco I, Bath SC, Rayman MP. Iodine as essential nutrient during the first 1000 days of life. *Nutrients* 2018;**10**:290.
- Venturi S, Donati FM, Venturi A, Venturi M, Grossi L, Guidi A. Role of iodine in evolution and carcinogenesis of thyroid, breast and stomach. *Adv Clin Pathol* 2000;**4**:11–17.
- Wang WJ, Zhang H, Chen ZQ, Zhang W, Liu XM, Fang JY, Liu FJ, Kwak-Kim J. Endometrial TGF- β , IL-10, IL-17 and autophagy are dysregulated in women with recurrent implantation failure with chronic endometritis. *Reprod Biol Endocrinol* 2019;**17**:2.
- Yang X, Gao T, Shi R, Zhou X, Qu J, Xu J, Shan Z, Teng W. Effect of iodine excess on Th1, Th2, Th17, and Treg cell subpopulations in the thyroid of NOD.H-2h4 mice. *Biol Trace Elem Res* 2014;**159**:288–296.
- Zhao X, Jiang Y, Wang L, Li Z, Li Q, Feng X. Advances in understanding the immune imbalance between T-lymphocyte subsets and NK cells in recurrent spontaneous abortion. *Geburtshilfe Frauenheilkd* 2018;**78**:677–683.
- Zhou SJ, Anderson AJ, Gibson RA, Makrides M. Effect of iodine supplementation in pregnancy on child development and other clinical outcomes: a systematic review of randomized controlled trials. *Am J Clin Nutr* 2013;**98**:1241–1254.