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ORIGINAL ARTICLE ***Reproductive endocrinology***

Thyroid function in neonates conceived after hysterosalpingography with iodinated contrast

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STUDY QUESTION: Does exposure to preconceptional hysterosalpingography (HSG) with iodinated oil-based contrast affect neonatal thyroid function as compared to iodinated water-based contrast?

SUMMARY ANSWER: Preconceptional HSG with iodinated contrast did not influence the neonatal thyroid function.

WHAT IS KNOWN ALREADY: HSG is a commonly applied tubal patency test during fertility work-up in which either oil- or water-based contrast is used. Oil-based contrast contains more iodine compared to water-based contrast. A previous study in an East Asian population found an increased risk of congenital hypothyroidism (CH) in neonates whose mothers were exposed to high amounts of oil-based contrast during HSG.

STUDY DESIGN, SIZE, DURATION: This is a retrospective data analysis of the H2Oil study, a randomized controlled trial (RCT) comparing HSG with the use of oil- versus water-based contrast during fertility work-up. After an HSG with oil-based contrast, 214 women had an ongoing pregnancy within 6 months leading to a live birth compared to 155 women after HSG with water-based contrast.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Of the 369 women who had a live born infant, 208 consented to be approached for future research and 138 provided informed consent to collect data on the thyroid function tests of their offspring (n = 140). Thyroid function tests of these children were retrieved from the Dutch neonatal screening program, which includes the assessment of total thyroxine (T4) in all newborns, followed by thyroid-stimulating hormone only in those with a T4 level of ≤ -0.8 SD score. Furthermore, amount of contrast medium used and time between HSG and conception were compared between the two study groups.

MAIN RESULTS AND THE ROLE OF CHANCE: Data were collected from 140 neonates conceived after HSG with oil-based (n = 76) or water-based (n = 64) contrast. The median T4 concentration was 87.0 nmol/l [76.0–96.0] in the oil group and 90.0 nmol/l [78.0–106.0] in the water group ($P = 0.13$). None of the neonates had a positive screening result for CH.
The median amount of contrast medium used was 9.0 ml [interquartile range (IQR), 6.0–11.8] in the oil-group and 10.0 ml [IQR, 7.5–14.0] in the water group ($P = 0.43$). No influence of the amount of contrast on the effect of contrast group on T4 concentrations was found (P-value for interaction, 0.37).

LIMITATIONS, REASONS FOR CAUTION: A relatively small sample size and possible attrition at follow-up are limitations of this study. Although our results suggest that the use of iodinated contrast media for HSG is safe for the offspring, the impact of a decrease in maternal thyroid function on offspring neurodevelopment could not be excluded, as data on maternal thyroid function after HSG and during conception were lacking.

WIDER IMPLICATIONS OF THE FINDINGS: As HSG with oil-based contrast does not affect thyroid function of the offspring, there is no reason to withhold this contrast to infertile women undergoing HSG. Future studies should investigate whether HSG with iodinated contrast influences the periconceptional maternal thyroid function and, consequently, offspring neurodevelopment.

[†]H2Oil Study Group members are listed in the Appendix.

STUDY FUNDING/COMPETING INTEREST(S): This study received no funding. The original H2Oil RCT was an investigator-initiated study that was funded by the two academic institutions (Academic Medical Center and VU University Medical Center) of the Amsterdam UMC. The funders had no role in study design, collection, analysis and intrepretation of the data. I.R. reports receiving travel fee from Guerbet. C.B.L. reports speakers fee from Ferring in the past and research grants from Ferring, Merck and Guerbet. K.D. reports receiving travel fee and speakers fee from Guerbet. B.W.M. is supported by a NHMRC Practitioner Fellowship (GNT1082548). B.W.M. reports consultancy for ObsEva, Merck KGaA and Guerbet and travel and research grants from Merck KGaA and Guerbet. V.M. reports receiving travel fee and speakers fee as well as research grants from Guerbet. The other authors do not report conflicts of interest.

TRIAL REGISTRATION NUMBER: Netherlands Trial Register NTR 7526 (Neonates born after the H2Oil study), NTR 3270 (original H2Oil study), www.trialregister.nl

Key words: neonatal screening / hypothyroidism / neonatal health / hysterosalpingography / iodine / oil-based contrast medium / water-based contrast medium

Introduction

Hysterosalpingography (HSG), to assess tubal patency, is a standard test during female fertility work-up. Although it was introduced as a diagnostic tubal patency test, it recently became clear that HSG increases ongoing pregnancy rates, especially after the use of oil-based contrast (Fang *et al.*, 2018; Wang *et al.*, 2019). All contrast media used for HSG are rich in iodine, with oil-based contrast containing more iodine (480 mg Iodine/ml) than water-based contrast (ranging from 240 to 300 mg Iodine/ml, depending on the manufacturer). In addition, the clearance of oil-based contrast in the abdomen is slower than that of water-based contrast (Brown *et al.*, 1949; Miyamoto *et al.*, 1995).

Previous studies found that HSG resulted in a long-lasting suppression of thyroid hormone synthesis in euthyroid women and, even more profoundly, in women with subclinical hypothyroidism (Mekaru *et al.*, 2008; Kaneshige *et al.*, 2015; So *et al.*, 2017). Subclinical hypothyroidism has been associated with an increased risk of pregnancy complications, including pre-eclampsia, perinatal mortality and (recurrent) miscarriage (van den Boogaard *et al.*, 2011; Korevaar *et al.*, 2019). Up until now two subsequent systematic reviews showed no increased risk of miscarriage or stillbirth in women exposed to oil-based contrast at HSG, which is reassuring (Fang *et al.*, 2018; Wang *et al.*, 2019).

There is some evidence showing that maternal iodine excess due to high dietary iodine intake or iodine-containing antiseptics may put offspring at risk of congenital hypothyroidism (CH) (l'Allemand *et al.*, 1983; Nishiyama *et al.*, 2004; Connelly *et al.*, 2012; Hamby *et al.*, 2018). To date, surprisingly few studies have focused on the impact of oil-based contrast during HSG on the neonatal thyroid function; all of them were conducted in Asian populations, who are known to consume diets rich in iodine. One study from Japan reported a high risk of CH (of 2.4%, as compared to 0.7% in the norm population) in neonates whose mothers were exposed to high amounts of oil-based contrast medium during HSG (Satoh *et al.*, 2015). The other studies described associations between HSG and the presence of fetal goiter or transient thyroid dysfunction at birth, but not with permanent thyroid dysfunction (Omoto *et al.*, 2013; Sasaki *et al.*, 2017). Indeed, neonates born to mothers exposed to HSG had a higher urinary excretion of iodine (Li *et al.*, 2018).

We recently published the results of a large randomized controlled trial (RCT; under the acronym H2Oil study) investigating the effects of oil- versus water-based contrast in women undergoing HSG as part of fertility work-up on live birth rates, indicating that the first was superior (Dreyer *et al.*, 2017). The present study investigated the thyroid function in their offspring at birth.

Materials and Methods

This is a retrospective data analysis of neonatal screening results for CH in the offspring of mothers participating in the H2Oil study who conceived within 6 months after HSG (NTR 3270). For this purpose, neonatal screening results were retrieved from the Dutch National Institute for Public Health and Environment (in Dutch: Rijksinstituut voor Volksgezondheid en Milieu). This specific study (NTR 7526) was approved by the institutional review board of the Amsterdam University Medical Centre—VU University Medical Centre, the Netherlands (reference 2018.463, dated 7 September 2018).

Participants

The H2Oil study is a multicenter RCT comparing oil-based contrast (Lipiodol® Ultra Fluid, Guerbet France, containing 480 mg Iodine/ml) with water-based contrast (Telebrix Hystero®, Guerbet France, containing 250 mg Iodine/ml) in women undergoing HSG during fertility work-up. Details of the H2Oil study have been published elsewhere (Dreyer *et al.*, 2017). Here, we only briefly describe the trial essentials. Infertile women between 18 and 39 years of age with spontaneous menstrual cycles were included in the H2Oil study. Known endocrine disorders (e.g. hyperthyroidism) were among the exclusion criteria. No routine screening of the thyroid function was performed.

A total of 1119 women were randomized to receive HSG with oil-based contrast (n = 557) or water-based contrast (n = 562) (Supplementary Figure S1). After HSG with oil-based contrast, within 6 months 214 women had an ongoing pregnancy leading to a live birth compared to 155 women after HSG water-based contrast (Dreyer *et al.*, 2017). Of these women, 208 (56%) had given permission to be approached for future research.

Parents were approached by postal mail, containing information on this study. For the retrieval of the neonatal screening results, both parents or legal guardians had to give written informed consent. Additionally, they were also asked to provide additional information of

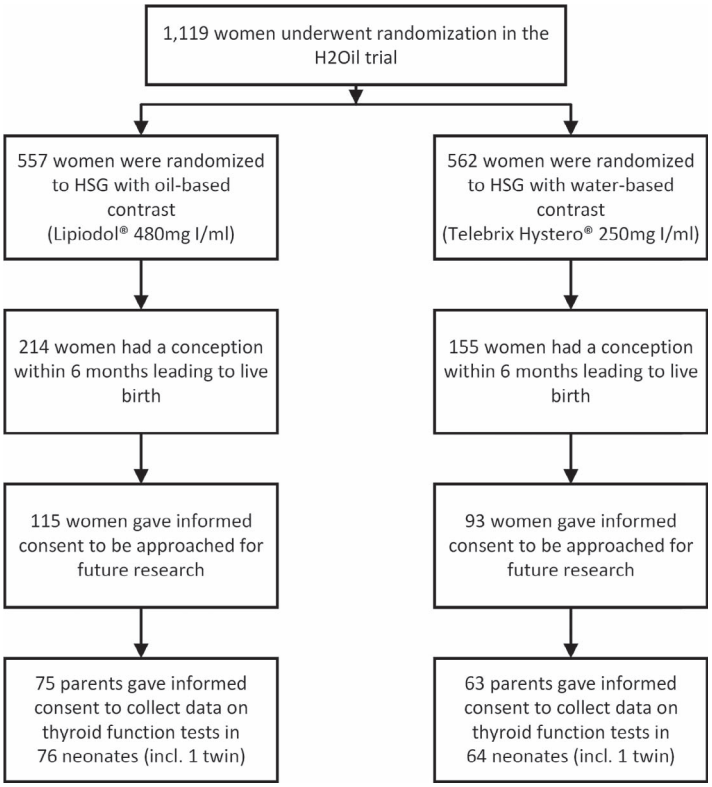

Figure 1 Flowchart of the study.

the medical history of their child, including previous or current thyroid hormone supplementation. Parents who did not respond within 2 weeks were sent a reminder.

Study outcomes

The main outcome was the neonatal total thyroxine (T4) concentration (nmol/l). Other outcomes were, if available, concentrations of thyroid-stimulating hormone (TSH) (mU/l) and thyroxine-binding globulin (TBG) (nmol/l).

Statistical analysis

Demographic characteristics of the study population were compared between the two study groups using the appropriate descriptive statistics. Categorical data were reported as absolute numbers with percentages (%)and continuous variables as medians with interquartile ranges (IQRs). Dichotomous outcomes were compared using the χ^2 test and continuous outcomes using the independent *t*-test or Mann–Whitney *U*-test as appropriate. We tested whether amount of contrast or time between HSG and conception modified the effect of contrast medium on neonatal T4 concentration. Effect modification by amount of contrast was tested using a linear regression model with T4 concentration as the dependent variable and amount of contrast, type of contrast (oil versus water) and their two-way interaction as independent variables. Effect modification by time between HSG and conception was tested using ANOVA with T4 concentrations as the dependent variable and time between HSG and conception, type of contrast (oil versus water) and their two-way interaction as independent variables. A *P*-value less than 0.05 was considered statistically significant. Boxplot and scatterplot were used to visualize the investigated associations. The IBM Statistical Package for Social Sciences version 26.0 was used for all statistical analyses (IBM Corp., USA).

Neonatal CH screening

The Dutch neonatal screening for CH is primarily based on T4 measurement in filter paper blood spots obtained during the heel prick at 4 to 7 days after birth. Details of the Dutch CH screening program have been described by (Kempers *et al.*, 2006). In summary, T4 concentrations are expressed as standard deviation score (SDS) from the daily mean. This is the standard screening procedure for CH in the Netherlands (Verkerk *et al.*, 2014). The daily means are used instead of population reference means, to account for fluctuation in laboratory measurements. If the T4 level is −0.8 SDS or less, the TSH concentration is measured as well. This is accompanied by TBG concentration when T4 is −1.6 SDS or less. Newborns with abnormal screening results are immediately referred to a pediatrician. In case of a dubious result, a second heel prick is performed, after which the child is referred if the result is dubious again or abnormal.

Results

In the oil group, 75 (65.2%) of the 115 parents gave informed consent to collect data on the thyroid function tests of their children (n = 76). In

Table I Clinical data of neonates conceived after hysterosalpingography (HSG) with the use of oil- or water-based contrast.

	Neonates born after HSG with		
	Oil contrast (n = 76)	Water contrast (n = 64)	*P*-value
Gestational age (weeks)	39.7 [39.0–40.9]	39.6 [38.6–40.7]	0.27
Birthweight[a] (grams)	3470 [3115–3855]	3460 [3065–3721]	0.67
Sex			
Male	38 (50)	30 (47)	0.71
Female	38 (50)	34 (53)	-
Current use of thyroid hormones	0 (0)	0 (0)	-
Neonatal screening[b]			
T4 (nmol/l)	87.0 [76.0–96.0]	90.0 [78.0–106.0]	0.13
T4 SDS[c]	−0.05 [−0.5–0.5]	0.2 [−0.3–0.9]	0.12
Amount of contrast (milliliter)[d]	9.0 [6.0–11.8]	10.0 [7.5–14.0]	0.43
Iodine dose (grams)[e]	4.3 [2.9–5.7]	2.5 [1.9–3.5]	0.001
Duration between HSG and conception (months)	2.3 [1.1–4.3]	2.1 [1.1–4.0]	0.83
Duration between HSG and delivery (months)	11.1 [9.6–13.0]	10.7 [9.8–12.9]	0.73

Data presented as median [quartiles] or number of women (%).
[a]Birth weight was missing in one neonate in the water group.
[b]Neonatal screening result was missing in one neonate in the water group, due to neonatal screening abroad.
[c]The concentration of T4 is expressed as standard deviation score (SDS) and is compared with the daily mean.
[d]Amount of contrast was missing in 32 in the oil group versus 39 women in the water group.
[e]The calculated iodine dose is strictly correlated to the amount of contrast medium used (Lipiodol® 480 mg Iodine/ml and Telebrix Hystero® 250 mg Iodine/ml).

the water group, 63 (67.7%) of the 93 parents gave informed consent to collect these data (n = 64; Fig. 1). The baseline characteristics were comparable between the two groups (Supplementary Table SI). Non-responders were not different from responders in baseline characteristics.

None of the neonates conceived after HSG with oil- or water-based contrast had a positive screening result for CH. Their data are presented in Table I. T4 concentrations and T4 SDSs were comparable between the two groups. None of the children were currently on thyroid hormone supplementation.

The amount of contrast used for HSG was reported in 44 women in the oil group versus 25 women in the water group. The median amount of contrast was 9.0 ml [IQR, 6.0–11.8] in the oil group and 10.0 ml [IQR, 7.5–14.0] in the water group ($P = 0.43$). Linear regression showed no influence of the amount of contrast on the effect of the contrast group on T4 concentrations (P-value for interaction 0.37). Figure 2a and b depict the association of neonatal T4 concentrations with the amounts of oil-based or water-based contrast used during HSG.

There was a significant difference in iodine dose between the two contrast media used (4.3 grams [IQR, 2.9–5.7] versus 2.5 [IQR, 1.9–3.5]; $P = 0.001$).

Time between HSG and conception was comparable between the oil and water groups (2.3 months [IQR, 1.1–4.3] and 2.1 months [IQR, 1.1–4.0]; $P = 0.83$). ANOVA showed no influence of time between HSG and conception on the effect of the contrast group on T4 concentrations (*P*-value for interaction 0.47).

Consequently, time between HSG and delivery did not differ between the two groups (11.1 months [IQR, 9.6–13.0] in the oil group versus 10.7 months [IQR, 9.8–12.9] in the water group; P-value 0.73).

However, in 13 neonates in the oil group and 7 neonates in the water group, T4 SDSs were ≤ -0.8 and, therefore, TSH was measured (relative risk (RR), 1.5; 95% CI, 0.7–3.6; $P = 0.32$). TSH concentrations were within normal limits for all 20 neonates with T4 SDSs ≤ -0.8. In one neonate in the oil group, TBG was additionally measured. Both TBG and T4/TBG ratio were within normal limits. Table II shows no differences in the oil group in amount of contrast or duration between HSG and conception among neonates with normal screening results and those with T4 values ≤ -0.8 SD, low enough to trigger TSH testing. We found comparable results for the water group (Table II).

Furthermore, no differences were seen in amount of contrast or duration between HSG and conception within the neonates with T4 ≤ -0.8 SDS in the oil group versus the water group.

Discussion

In this study, we found that preconceptional exposure to an HSG with oil-based or water-based contrast did not result in decreased thyroid function in the offspring. In addition, we did not find an impact of the amount of contrast used or the duration between HSG and conception on neonatal T4 concentration between the treatment arms. Our results are not in line with previous studies in East Asian populations.

A Japanese study found a higher frequency of thyroid dysfunction in newborns conceived after HSG compared to normative data (2.4% versus 0.7%; Satoh *et al.*, 2015). In this study, mothers giving birth

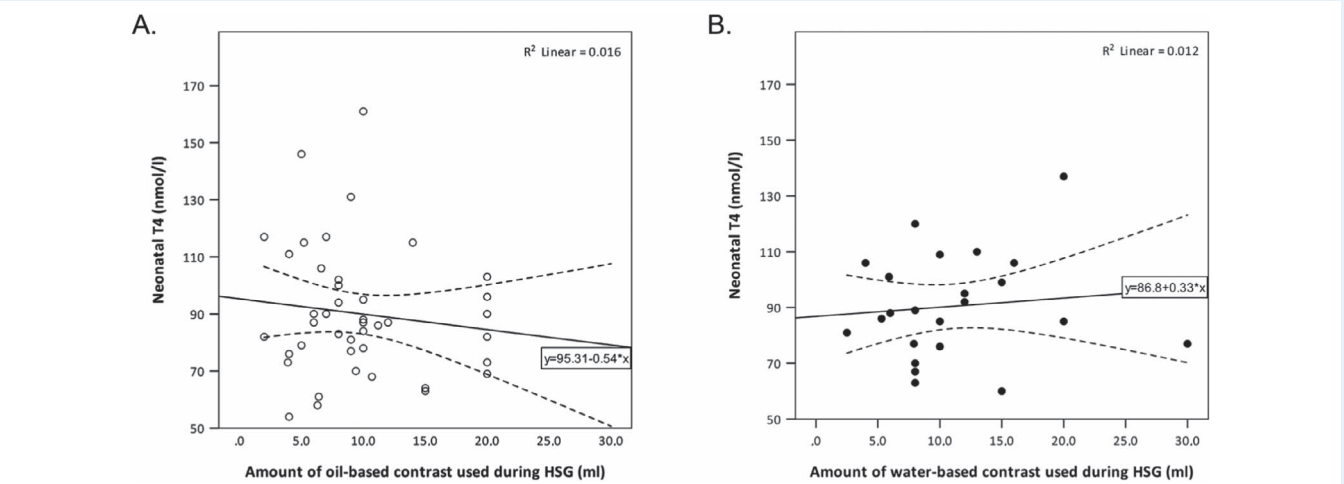

Figure 2 Association of neonatal T4 level with the amount of contrast used for (A) oil-based contrast and (B) water-based contrast. The scatterplots show the association of neonatal T4 concentrations with the amount of (A) oil-based contrast versus (B) water-based contrast used during HSG. Both scatterplots show the linear regression lines (solid lines) with their uncertainty (dotted lines).

Table II Clinical data of neonates with normal T4 or T4 ⩽ −0.8 SD in the oil (n = 76) and water (n = 64) group.

	Neonates in the oil group			Neonates in the water group		
	Normal T4 > − 0.8 SD (n = 63)	T4 ≤ − 0.8 SD (n = 13)	*P*-value	Normal T4 > − 0.8 SD (n = 56)	T4 ≤ − 0.8 SD (n = 7)	*P*-value
Neonatal screening						
T4 (nmol/l)	88.0 [81.0–102.0]	61.0 [54.5–70.5]	-	92.0 [84.0–106.0]	68.0 [63.0–71.0]	-
T4 SDS[f]	0.2 [−0.2–0.7]	−1.1 [−1.4–−0.9]	-	0.3 [−0.2–1.0]	-0.9[−1.1– −0.8]	-
TSH[g] *(mU/l)*	-	2.0 [1.0–2.5]	-	-	1.0 [1.0–2.0]	-
Amount of contrast (ml)[h]	9.0 [6.0–11.0]	10.0 [6.3–20.0]	0.53	10.0 [7.0–14.0]	8.0 [8.0–11.5]	1.00
Iodine dose (grams)[i]	4.3 [2.9–5.3]	4.8 [3.0–9.6]	0.53	2.5 [1.7–3.5]	2.0 [2.0–2.9]	1.00
Duration between HSG and conception (months)	2.4 [1.1–4.5]	1.9 [0.7–3.5]	0.36	2.2 [1.1–4.1]	1.9 [1.2–2.9]	0.58
Duration between HSG and delivery (months)	11.2 [9.6–13.3]	10.8 [9.1–12.1]	0.16	10.9 [9.8–13.0]	10.6 [9.7–11.6]	0.56

Data presented as median [quartiles].
[f]The concentration of T4 is expressed as SDS and is compared with the daily mean.
[g]T4 values ≤ − 0.8 SD, low enough to trigger TSH testing.
[h]Amount of contrast was missing in 26 versus 6 women in the oil-group and 35 versus 4 women in the water-group.
[i]The calculated iodine dose is strictly correlated to the amount of contrast medium used (Lipiodol® 480 mg Iodine/ml and Telebrix Hystero® 250 mg Iodine/ml).

to offspring with thyroid dysfunction had been exposed to a higher amount of contrast during HSG (median of 20 ml versus 8 ml), although used amount was only available for 112 out of 212 neonates with normal thyroid function and for 3 out of 5 neonates with thyroid dysfunction (Satoh *et al.*, 2015). To the best of our knowledge, only two Japanese cases with fetal goiter after maternal HSG were reported (Omoto *et al.*, 2013; Sasaki *et al.*, 2017), although according to Omoto *et al.* (2013) 'at least 17 cases of transient hypothyroidism in a fetus after HSG have been reported in Japanese literature since 1990'. In one of these fetuses, the goiter resolved during pregnancy and the thyroid function tests were normal at birth (Sasaki *et al.*, 2017). In the other the fetal goiter persisted and overt hypothyroidism was noted at birth. This was followed by a spontaneous resolution of the goiter by 4 weeks post-partum along with normalization of thyroid function tests in the preceding weeks (Omoto *et al.*, 2013). None of the children in our sample were diagnosed with goiter as newborns.

As stated earlier, all studies conducted thus far were limited to East Asian populations. There is a striking difference in background risk for CH between Japan and the Netherlands, i.e. 0.7% in Japan versus 0.05% in the Netherlands (Tokyo Health Service Association, 2010; Dutch National Institute for Public Health and Environment, 2014). Among the possible explanations for this difference is the high consumption of iodine-rich foods (i.e. seaweed) in Japan. It has been estimated that the iodine intake of pregnant women in Japan is approximately 3–4 times as

high as the World health Organization recommendation (World Health Organization, 2007; Fuse et al., 2013).

Strengths and limitations

The current study has several strengths and limitations. The major strengths are that this study was based on a large multicenter RCT and had included a large majority of Caucasian women. Additionally, in contrast to other countries, which generally have TSH-based screening programs, the Dutch neonatal screening program for CH is T4-TSH-TBG based, being able to detect CH of both central and thyroidal origin. The amount of contrast used during HSG was reported, instead of the calculated iodine dose, as the amount of contrast is relevant for clinicians in daily practice and iodine dose is strictly correlated to the amount of contrast used.

Limitations of our study are the relatively small sample size and attrition at follow-up. This might obscure a possible relation between the type of contrast medium and the presence of CH if women with excessive iodine exposure selectively declined to participate. However, a non-response analysis showed that responders and non-responders did not differ in a number of the baseline characteristics, implicating that non-response bias is unlikely to have materially influenced our observations, although the amount of contrast used was not known from all participants. The H2Oil RCT was not powered to study the safety in neonates of the different types of iodinated contrast media during HSG. Nonetheless, data regarding the neonatal thyroid function are reliable even though they were collected retrospectively.

Furthermore, only offspring conceived within 6 months after HSG were included (Dreyer et al., 2017). Offspring conceived between 6 months and 5 years after HSG, who also took part in the H2Oil follow-up study, were not contacted for this specific study (van Rijswijk et al., 2018). It is unlikely that iodinated contrast could still affect the offspring's thyroid function when more time than 6 months has elapsed between HSG and conception (Kaneshige et al., 2015; So et al., 2017).

Our study did not include an assessment of the maternal thyroid function after HSG or during conception. Consequently, it was impossible to study the impact of a decrease in the maternal thyroid function on offspring neurodevelopment. Studies in East Asian populations demonstrated that HSG could result in a long-lasting suppression in thyroid hormone synthesis in euthyroid women and, even more profoundly, in women with subclinical hypothyroidism (Mekaru et al., 2008; Kaneshige et al., 2015; So et al., 2017). Furthermore, the use of iodine-rich products preconceptionally during pregnancy or after delivery was not registered, which could potentially influence our findings.

Implications

Overexposure to iodine may result in a sudden cessation of thyroid hormone synthesis, a phenomenon called the Wolff–Chaikoff effect (Eng et al., 1999). This protective mechanism works for a couple of days, after which thyroid hormone synthesis is resumed. However, during prolonged exposure to excess iodine, the thyroid gland is unable to escape from the Wolff–Chaikoff effect, resulting in a long-lasting suppression of thyroid hormone synthesis (Wolff et al., 1949; Markou et al., 2001; Leung and Braverman, 2012).

From the second trimester of pregnancy the fetal thyroid gland starts to produce thyroid hormones. Therefore, during early embryonic development the fetal brain depends entirely on the supply of maternal thyroid hormones (Contempre et al., 1993; Burrow et al., 1994). Consequently, overexposure to iodine may not only disrupt fetal brain development through inhibition of fetal thyroid hormone synthesis but also through its effects on the maternal thyroid gland. This is suggested by an increasing body of evidence demonstrating that children born to mothers with decreased thyroid function during the first half of pregnancy had reductions in the achievement of developmental milestones, IQ score, reaction time, scholastic performance and attention, although the evidence was not unequivocal (Haddow et al., 1999; Pop et al., 1999; Smit et al., 2000; Pop et al., 2003; Oken et al., 2009; Henrichs et al., 2010; Li et al., 2010; Craig et al., 2012; Noten et al., 2015; Oostenbroek et al., 2017; Thompson et al., 2018). Therefore, monitoring of the maternal thyroid function after HSG might seem warranted, but at this point no definite conclusion can be drawn.

Conclusion

In contrast to previous research in East Asian populations, we found that preconceptional HSG with iodinated contrast did not influence neonatal thyroid function. Although this suggests that iodinated contrast media are safe for the offspring, indirect effects on neurodevelopment (through inhibition of maternal thyroid hormone synthesis) could not be excluded and warrant further investigation. Meanwhile, there is no reason to withhold HSG with oil-based contrast to infertile women. We recommend keeping the amount of contrast used as low as possible.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

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Authors' roles

N.W., K.D., V.M., M.J.J.F., C.B.L. and B.W.J.M. designed this study. N.W. and M.P. collected the data. N.W. performed the analysis and wrote the first draft. N.W., I.R., C.K., C.B.L., B.W.J.M., K.D., M.J.J.F. and V.M. interpreted the data and critically discussed and structured the manuscript. N.W. is the first author of this manuscript. B.W.J.M. was the principle investigator of the original H2Oil study. K.D. and J.R. coordinated the original H2Oil study and collected data regarding

the women in the original H2Oil study. All authors discussed and commented on the manuscript. All authors have approved the final draft of the manuscript.

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Conflict of interest

I.R. reports receiving travel fee from Guerbet. C.B.L. reports speakers fee from Ferring in the past and research grants from Ferring, Merck and Guerbet. K.D. reports receiving travel fee and speakers fee from Guerbet. B.W.M. is supported by a NHMRC Practitioner Fellowship (GNT1082548). B.W.M. reports consultancy for ObsEva, Merck KGaA and Guerbet and travel and research grants from Merck KGaA and Guerbet. V.M. reports receiving travel fee and speakers fee as well as research grants from Guerbet. The other authors do not report conflicts of interest.

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