Developmental milestones at one year for the offspring of mothers with congenital hypothyroidism: a population-based study

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Abstract

Objective: Maternal thyroid dysfunction during pregnancy is associated with neurodevelopmental impairment in the offspring. No data are currently available for the offspring of patients treated early for congenital hypothyroidism (CH). The aim of this study was to investigate motor and language milestones at one year of age in a population-based registry of children born to young women with CH.

Design and methods: We assessed 110 children born to mothers with CH, and 1367 children from the EDEN French population-based birth cohort study prospectively, at the age of one year, with identical questionnaires. Outcomes were assessed in terms of scores for childhood developmental milestones relating to mobility, motor coordination, communication, motricity and language skills.

Results: After adjustment for confounding factors, children born to mothers with CH were found to have a higher risk of poor motor coordination than those of the EDEN cohort (OR: 4.18, 95% CI: 2.52–6.93). No differences were identified for the other four domains investigated. Children born to mothers with gestational diabetes have a higher risk of low motor coordination score than their peers (OR: 2.10, 95% CI: 1.21–3.66). Children born to mothers with TSH ≥ 10 IU/L during the first six months of pregnancy were more likely to have low motricity or communication skills scores than those born to mothers with lower TSH concentrations (56% vs 21% for each score, $P < 0.04$).

Conclusions: Maternal CH may have slight adverse effects on some developmental milestones in the child at one year of age, particularly for children born to mothers with uncontrolled hypothyroidism. However, it remains unclear whether these adverse effects modify subsequent neurodevelopment.

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Introduction

Adequate thyroid hormone (TH) levels are essential for human neurodevelopment during fetal and early postnatal life. During the first trimester of gestation, the only source

of TH is the mother, with fetal thyroid function beginning at 12–14 weeks of gestation. However, the fetus continues to receive THs from the mother until term, and these maternal

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hormones play a protective role in fetal neurodevelopment, particularly during the first half of pregnancy (1). Maternal thyroid dysfunction during pregnancy is associated with adverse pregnancy and neonatal outcomes and poor neurocognitive outcomes in the child, particularly if the dysfunction occurs early in pregnancy (2, 3, 4, 5).

Congenital hypothyroidism (CH) affects one in every 3000 newborns in most countries. Its neurodevelopmental prognosis has been greatly improved by early neonatal management since the introduction of neonatal screening. If treatment is initiated late, the affected child may suffer severe brain damage. As a result, few patients with CH born before the introduction of neonatal screening went on to have children. We recently reported the first cohort study on pregnancy outcome in the CH patients who were treated early. We found that these patients had a higher risk of gestational hypertension, emergency cesarean delivery, induced labor for vaginal delivery and preterm delivery than the reference population (6). Disease etiology and severity were not associated with a higher risk of adverse outcomes. We also demonstrated that, although TH requirements and levothyroxine (L-T4) dose increased during pregnancy, serum thyroid-stimulating hormone (TSH) concentration was high ($\text{TSH} \geq 5 \text{ IU/L}$) in the first or second trimester in 40% of the pregnancies for which TSH assays were carried out. Moreover, in the same cohort, about half the patients reported no TSH test results at any time during pregnancy, suggesting that follow-up was non-optimal or that compliance with treatment was poor in these women. High serum TSH concentrations ($\text{TSH} \geq 10 \text{ IU/L}$) during the first three to six months of pregnancy were associated with a higher risk of preterm delivery and fetal macrosomia (6).

In this context, the aim of this study was to describe the main developmental milestones reached at one year of age by the offspring of women with CH, comparing these results with those for children from a population-based cohort. We also investigated whether the developmental milestones of these children were related to treatment quality before and during pregnancy and to the disease severity of maternal CH.

Patients and methods

Subjects

CH group

This cohort of young adults was established for an investigation of the long-term consequences of being born with CH and has been described in detail elsewhere

(7, 8). It includes all patients ($n=1842$) diagnosed with primary CH in France in the decade following the introduction of neonatal CH screening (1978–1988). A baseline health questionnaire was sent by regular mail and was completed by 1202 participants (in 2007–2008). All patients completing this questionnaire were then sent a self-administered questionnaire focusing on fecundity in each of the next two years. All women with CH declaring a pregnancy during this three-year period were invited, at the time of pregnancy declaration, to participate in this prospective study and to complete a questionnaire on pregnancy outcome. They were asked to return the pregnancy questionnaire within three months of the end of the pregnancy. This additional prospective study included all pregnancies ending after the completion of the initial questionnaire in 2007–2008. We also conducted a retrospective study, including all pregnancies ending before the completion of the first questionnaire. For the 570 pregnancies declared by 336 of the 860 women with CH, 381 pregnancies ($n=207$ retrospective, $n=174$ prospective) ended in a singleton delivery after at least 22 weeks of gestation, with the newborns weighing at least 500g; three pregnancies produced twins. There were, therefore, 387 newborns in total. The other 186 pregnancies ended in a voluntary termination ($n=104$), spontaneous miscarriage ($n=77$), abortion for medical reasons ($n=4$) or outcome was not determined ($n=1$) (6). All women with CH with children reaching the age of one year during the study period ($n=174+43=217$) were then asked to complete a questionnaire on the health status of the child at the age of one year (2007–2011) (Fig. 1).

Study participation

Questionnaires were completed prospectively for the 125 singletons reaching the age of one year during the study period who were born to women with CH agreeing to participate during the prospective ($n=89$) or retrospective ($n=36$) period (see flowchart on Fig. 1). No difference was found between the participating mothers and those who did not complete the questionnaire ($n=92$) in terms of the etiology of hypothyroidism, age, education level, term at delivery of the child, prematurity, sex and birth weight of the child, presence or absence of gestational diabetes, hypertension during pregnancy, but the participants were less likely to have undergone cesarean section and more likely to have undergone induced labor than the non-participants (data not shown).

We selected one sibling per participating family (10 children were excluded and the child closest in age to

Figure 1

Flow chart of the study. Selection process for study participation for the EDEN cohort and the children of women with CH..

one year at the time of questionnaire completion was retained). We excluded children with a history of chronic disease ($n=2$; 1 case of craniosynostosis and 1 case of CH with athyreosis), and children with missing data ($n=3$; not all scores were available). The study population of children born to mothers with CH consisted of 110 children. Data for covariates were missing for five of these children, so the final multivariate analysis included 105 children (Fig. 1).

The study was approved by the institutional review board of Paris North Hospitals, Paris 7 University, Assistance Publique Hôpitaux de Paris.

The EDEN mother-child cohort

The EDEN cohort was used as a control group. This group was established for an ongoing birth cohort study investigating the outcome of children in the general population (9). Participants were recruited between

2003 and 2006 from the pregnant women (24 weeks of amenorrhea) followed in two university hospital maternity units, in Poitiers and Nancy (France). The exclusion criteria were multiple pregnancies (e.g. twins), diabetes diagnosed before pregnancy, illiteracy or moving out of the region within the next three years. Overall, 53% of the women fulfilling the inclusion criteria agreed to participate. In total, 2002 women were included in the study, and 1907 were still being followed up at the time of the delivery.

Study participation

We excluded 92 children because of the presence or a history of thyroid disorder in the mother. Between birth and the age of one year, eight children died, 151 were lost to follow-up, and 95 did not attend the clinical examination at the age of one year. Thus, for 1561 infants of the EDEN study, an examination was performed by

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a trained midwife or a questionnaire completed by the parents was provided, when the child was one year old. Complete developmental milestone scores were available for 1410 of these children, and no data were missing for covariates for 1367 children (Fig. 1).

The study was approved by the Ethics Committee of Kremlin-Bicêtre Hospital and by the French Data Protection Authority. Written consent was obtained from the mothers for both themselves and their offspring.

Data collection

CH group

For the mothers with CH, basic neonatal registration was completed at diagnosis, with further surveys during early adulthood (7, 8) and pregnancy (6). Key variables relating to disease severity (CH etiology, bone maturation delay at knee epiphyseal ossification centers and serum-free T4 (FT4) concentration at diagnosis), thyroid function and treatment quality during early adulthood and during pregnancy were defined *a priori*, as previously reported (8, 10). We assessed the quality of thyroid function control (TSH levels) and L-T4 dose for the 110 women with CH, before pregnancy and in the first, second and third trimesters of pregnancy. The questionnaire for assessing the outcome of the child included items dealing with sociodemographic characteristics, chronic medical problems and the assessment of developmental milestones at 12 months.

The EDEN population

Sociodemographic data were collected during the first clinical examination of the mother, between 24 and 28 weeks of gestation and were updated with a self-administered questionnaire completed by the parents at one year. Clinical and health data relating to pregnancy, delivery and the newborn were collected from the obstetric and pediatric records (11).

Assessment of developmental milestones at 12 months

For both the CH and EDEN cohorts, the assessment included items from the second version of the French Brunet-Lezine II developmental test created by Josse (12) and from the Bayley Scales of Infant Development (13). Most of the items were identical for the two populations and were grouped into five domains: mobility, coordination, language, motricity and communication. For the CH cohort, all questionnaires were completed

by the parents. For the EDEN cohort, the first three domains were assessed with a questionnaire completed by the midwife during a semi-directed interview with the mother. The other two items were assessed from the questionnaire completed by the parents when the child was one year old (11). Scores were generated by summing the dichotomous responses to each item (Supplementary Table 1, see section on supplementary data given at the end of this article).

The mean was imputed for missing items when there were no more than two missing items for the coordination, motricity or communication scores for a particular child, and no more than three such items for the mobility and language scores. We set a threshold for each score, for comparisons of a lower development level with all the others. This threshold was based on the 20th percentile of the distribution of each composite score, to ensure that sufficient numbers of children were retained in the groups and to maintain statistical power. However, for coordination scores, the 20th percentile was not specific enough (i.e. it actually included more than 50% of the children, due to the large number of ties), so we used the 10th percentile instead.

Other data collected

The following common information was collected for the mothers of the CH and EDEN cohorts: age at delivery, educational achievement (more or less than 12 years of schooling), parity (primiparous vs others), hypertension during pregnancy, gestational diabetes, smoking, mode of delivery (spontaneous or induced vaginal delivery, programmed or emergency cesarean delivery) and marital status (living with or without a partner when the child was one year old). We collected the following information for the child: sex, birth weight, prematurity (<37 weeks), exact age at follow-up assessments.

Statistical analysis

The results are expressed as means ($\pm$ S.E.M.) or medians (25–75th percentile) for quantitative variables, and as absolute numbers and percentages for qualitative variables. We first compared the offspring of the mothers in the CH cohort (exposed) with those from the EDEN cohort (non-exposed) for all maternal, delivery and child characteristics, in chi-squared and unadjusted Student's *t* tests. Developmental milestone scores were also described and compared between the two populations in chi-squared tests. We used nonparametric Fisher's exact tests

to compare percentages for isolated items. The populations included in and excluded from the analysis were also compared within each cohort (CH or EDEN). Multivariate logistic regression models were used to predict the risk of each psychomotor and language outcome (low scores, as defined earlier). The cohort study and the adjustment variables were entered into the models as independent variables. Adjustment factors were selected for inclusion in the models if they differed between the CH cohort and a national representative sample of pregnancies (6) or were significantly ($P < 0.10$) associated with outcome in unexposed children (i.e. the children of the EDEN cohort).

We then compared developmental milestones according to thyroid function. We first compared women with serum TSH concentrations ≥ 5 mIU/L with women with serum TSH concentrations of 0.1–4.9 mIU/L, during each trimester of pregnancy. We then compared women with at least one serum TSH concentration ≥ 10 mIU/L during the first semester of pregnancy with those for whom all serum TSH concentrations were between 0.1 mIU/L and 9.9 mIU/L during this period. We used Fisher's exact tests for this comparison, due to the small numbers of subjects in each group.

All statistical analyses were performed with SAS 9.3 software (SAS Institute Inc, Cary, North Carolina).

Results

The characteristics of the study population are summarized in Table 1. Women with CH had a lower education level, were more likely to be younger and less likely to be living with partners than the women from the EDEN cohort. At the follow-up assessment, the children from CH mothers were slightly older, more likely to be looked after by their mothers or another family member and were more likely to be the first child born to the mother than the children in the EDEN cohort.

Comparisons of the characteristics of the mother and child between children included in and excluded from analyses within the CH and EDEN populations are shown in Supplementary Tables 2 and 3, respectively. The included mothers from the CH and the EDEN cohorts were less likely to be looking after the child themselves during the day, the included mothers from the CH group were more likely to be primiparous and those from the EDEN cohort were slightly older and had higher education levels than those excluded.

The one-year developmental milestone scores are described, with their thresholds, in Table 2, separately for the offspring of mothers with CH and for the children of the EDEN cohort. The rates of low motricity

Table 1 Maternal and infant characteristics, by study population, EDEN vs congenital hypothyroidism. Data are presented as % (n) or mean $\pm$ S.E.M.

	All (n=1472)	EDEN (n=1367)	CH (n=105)	P
Female	47.1 (693)	47 (643)	47.6 (50)	0.91
Exact age of the child at examination (months)	12.2 $\pm$ 0.02	12.2 $\pm$ 0.01	12.5 $\pm$ 0.14	<0.0001
Prematurity (yes)	5.8 (85)	5.5 (75)	9.5 (10)	0.09
Birth weight (g)	3292.1 $\pm$ 13.0	3292.6 $\pm$ 13.5	3285.9 $\pm$ 50.5	0.90
Main daytime caregiver				0.049
Nursery or childminder	56.8 (836)	57.6 (788)	45.7 (48)	
Family	10.1 (149)	9.8 (134)	14.3 (15)	
Mother	33.1 (487)	32.6 (445)	40 (42)	
Maternal age at delivery (years)	30.1 $\pm$ 0.12	30.3 $\pm$ 0.13	26.8 $\pm$ 0.25	<0.0001
Primiparity (yes)	46.8 (689)	46.2 (631)	55.2 (58)	0.07
Hypertension during pregnancy (yes)	6.8 (100)	6.7 (91)	8.6 (9)	0.45
Gestational diabetes (yes)	6.6 (97)	6.6 (90)	6.7 (7)	0.97
Maternal smoking during pregnancy (yes)	23.0 (338)	23.2 (317)	20 (21)	0.46
Delivery mode				0.28
Spontaneous vaginal delivery	67.1 (988)	67.6 (924)	61.0 (64)	
Induced vaginal delivery	17.4 (256)	17.2 (235)	20.0 (21)	
Programmed cesarean delivery	6.7 (98)	6.7 (92)	5.7 (6)	
Emergency cesarean delivery	8.8 (130)	8.5 (116)	13.3 (14)	
Living with a partner at follow-up (yes)	76.6 (1127)	77.5 (1059)	64.8 (68)	0.003
Maternal education (>12 years)	56.4 (830)	57.4 (784)	43.8 (46)	0.007
Thyroid disease		NA		
Athyreosis		–	30.5 (32)	
Ectopic gland		–	53.3 (56)	
Eutopic gland		–	13.3 (14)	
Unknown		–	2.9 (3)	

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Table 2 Development milestone scores: low score rates by study population, and odds ratios from multivariate logistic models. The EDEN population was used as the reference population.

Outcome	Range	Threshold	Cases % (n)	EDEN (n=1367) % (n)	CH (n=105) (7.1%) % (n)	P ^a	Adjusted OR* (95% CI)	P
Mobility	0–10	≤5	25.2 (371)	25.9 (354)	16.2 (17)	0.03	0.597 (0.33–1.07)	0.083
Motor coordination	0–5	≤2	10.9 (161)	9.7 (132)	27.6 (29)	<0.0001	4.181 (2.52–6.93)	<0.0001
Language	0–8	≤5	28.4 (418)	29.1 (398)	19.0 (20)	0.03	0.735 (0.43–1.26)	0.26
Motricity	0–6	≤3	26.0 (383)	26.2 (358)	23.8 (25)	0.64	0.988 (0.59–1.64)	0.96
Communication	0–6	≤4	25.2 (371)	25.5 (348)	21.9 (23)	0.48	0.988 (0.58–1.67)	0.96

^aFisher's exact test; *OR adjusted for sex, age, prematurity, type of delivery, birth weight, main daytime time caregiver, maternal age at delivery, Primiparity, hypertension during pregnancy, gestational diabetes, maternal smoking during pregnancy, living with a partner, maternal education.

and communication scores did not differ significantly between these two populations. However, the offspring of mothers with CH were more likely than the children of the EDEN cohort to have low motor coordination skills, but less likely to have low mobility and language skills at 12 months of age.

After adjustment of the multivariate logistic models for relevant factors, the differences for mobility and language scores were no longer significant. The OR of the children of mothers with CH having a low score for motor coordination relative to children from the EDEN cohort was high (OR: 4.18; 95% CI: 2.52–6.93) and significant ($P<0.0001$). Similar results were obtained when the analysis was restricted to children of mothers with well-controlled CH (for motor coordination, OR: 3.46; 95% CI: 1.6–7.51) ($P<0.001$). The results of the multivariate logistic regression model for motor coordination are

shown in Table 3. Exact age at assessment and gestational diabetes were the other two factors significantly associated with outcome. Children born to mothers with gestational diabetes had a higher risk of low motor coordination score than their peers (OR (95% CI)=2.10 (1.21–3.66)). None of the other characteristics of the pregnancy, the mother or the child considered were associated with the risk of poor motor coordination at 12 months of age.

The results of thyroid tests and L-T4 dose before and during pregnancy are described for mothers with CH in Table 4. In 36 pregnancies, women with CH declared no TSH determination results during pregnancy. Serum TSH concentration was high ($TSH \geq 5$ mIU/L) during the first trimester of pregnancy in 18 women and during the second trimester of pregnancy in 17 women, corresponding to 25% and 26%, respectively, of the women for whom TSH assays were carried out. Overall, 41% ($n=31$) of these

Table 3 Multivariate logistic regression model for the risk of poor coordination at the age of one year.

	OR	95% CI	P
Cohort Study: CH vs EDEN	4.181	(2.52–6.93)	<0.0001
Female	0.995	(0.71–1.4)	0.98
Exact age (days)	0.989	(0.98–1)	0.023
Prematurity (yes)	1.584	(0.78–3.23)	0.21
Birth weight (100 g)	0.978	(0.94–1.02)	0.27
Main daytime caregiver			
Nursery or childminder	0.901	(0.61–1.34)	0.61
Family	0.808	(0.43–1.53)	0.51
Mother	1		
Maternal age at delivery (5 years)	1.103	(0.89–1.36)	0.37
Primiparity (yes)	0.969	(0.66–1.41)	0.87
Hypertension during pregnancy (yes)	0.731	(0.36–1.49)	0.39
Gestational diabetes (yes)	2.102	(1.21–3.66)	0.009
Delivery mode			
Spontaneous vaginal delivery	1		
Induced vaginal delivery	1.032	(0.65–1.63)	0.89
Programmed cesarean delivery	1.063	(0.55–2.05)	0.86
Emergency cesarean delivery	1.139	(0.63–2.06)	0.67
Maternal smoking during pregnancy (yes)	0.822	(0.53–1.28)	0.38
Living with partner (yes)	1.181	(0.77–1.8)	0.44
Maternal education: (>12 years)	1.069	(0.94–1.21)	0.30

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Table 4 Thyroid function and levothyroxine dose for women with congenital hypothyroidism ($n=110$), before pregnancy, and in the first, second and third trimesters of pregnancy. Data are presented as % (n) or median (25–75th percentile).

	At the time of the baseline questionnaire*	First trimester	Second trimester	Third trimester
TSH (mIU/L)	0.8 (0.2–1.7) ($n=42$)	3 (1.3–4.8) ($n=73$)	3 (1.7–5) ($n=66$)	1.9 (0.9–3.3) ($n=57$)
TSH < 0.1	16.7 (7)	6.8 (5)	3.0 (2)	1.8 (1)
TSH 0.1–4.9	78.6 (33)	68.5 (50)	71.2 (47)	89.5 (51)
TSH 5.0–9.9	2.4 (1)	19.2 (14)	18.2 (12)	5.3 (3)
TSH ≥ 10	2.4 (1)	5.5 (4)	7.6 (5)	3.5 (2)
Levothyroxine dose ($\mu\text{g/day}$)	137 (125–163) ($n=54$)	150 (133–175) ($n=102$)	162 (150–183) ($n=103$)	175 (150–200) ($n=102$)

*In the three months before pregnancy.

women had at least one high TSH concentration during pregnancy. Levothyroxine requirements increased from a median of 137 (125–163) before pregnancy to 175 (150–200) μg per day during the third trimester of pregnancy.

No association was found between any of the five developmental domains and any of the parameters relating to the quality of thyroid function control in the mother at any period considered, as assessed with a threshold of 5 mIU/L for serum TSH concentration (values above this threshold being considered to be high, whereas those between 0.1 and 4.9 mIU/L were considered to be normal (results not shown)).

Nine women had at least one very high serum TSH value (≥ 10 mIU/L) during the first semester of pregnancy, corresponding to 12% of women with at least one TSH assay. The offspring of these mothers were more likely to have low scores for motricity and communication skills than their 62 peers with serum TSH concentrations from 0.1 to 9.9 mIU/L (56 vs 21%, $P<0.04$, for both motricity and communication skills).

None of the developmental outcome scores was associated with CH severity in the mother, as assessed by the type of CH (athyreosis, ectopic or eutopic gland), bone maturation delay at the time of diagnosis (with at least one knee epiphyseal ossification center absent in the most severe forms) and serum FT4 levels at diagnosis (data not shown).

Discussion

This prospective observational study is, to our knowledge, the first to have examined the neurodevelopmental outcomes of children born to mothers with CH from a national cohort study of women treated early, through the neonatal screening program. Milestones for mobility, communication, motricity and language skills were similar,

but there was a higher risk of low motor coordination score in one-year-old children born to mothers with CH than in children of the same age in the control population. Gestational diabetes was also strongly associated with this outcome, as it more than doubled the risk of low motor coordination score, but this condition was taken into account in the model and was not responsible for the association between CH and coordination.

Previous studies have shown a slightly low total motor impairment score, including manual dexterity during childhood, in patients treated early for severe CH (14, 15, 16), but such impairment is unlikely to be involved in the association found in our study.

Other observational studies have suggested an association between gestational diabetes, particularly for women whose blood glucose levels did not remain optimal and impaired neurodevelopment in the offspring at the age of one to two years, with significant heterogeneity in children assessed at the ages of 3–12 years (17). These findings have led to the hypothesis that gestational diabetes may have a major impact on the cognitive function of the offspring very early in life, with this impact gradually decreasing as the child grows up. No causal relationship has been established, but it has been suggested that the mother being overweight or obese may have a synergistic effect in the triggering of adverse neurodevelopmental outcomes in children (17, 18). It should be borne in mind that women with CH are more likely to be overweight/obese than the general population (6).

We can speculate that this impairment at one year of age may have little impact on subsequent cognitive development, as recently observed in the children from the EDEN cohort studied longitudinally for five to six years. In the EDEN study, developmental milestones at one year predicted only a small proportion of the intellectual quotient (IQ) at the age of five to six years; early language skills, which were preserved in our population of children

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born to mothers with CH, were stronger predictors of IQ than the other cognitive domains considered (19).

Another interesting finding of our study, albeit based on the analysis of only a small number of children, was the association between low motricity and communication skill scores at the age of one year in the child and the obtainment of at least one serum TSH concentration ≥ 10 mIU/L during the first semester of pregnancy. Smaller increases in serum TSH levels had no such effect. No other association was observed with subclinical hypothyroidism (5–9.9 mIU/L) at any time during pregnancy, inadequate treatment before pregnancy (considered to reflect chronic treatment inadequacy) or disease etiology or CH severity in the mother.

These results should be considered in light of the known importance of thyroid control in women with acquired hypothyroidism, particularly during the first half of pregnancy, as a risk factor for neurodevelopmental impairment, as shown in most previous studies (2, 4, 5, 20, 21, 22, 23). The evidence of a link is weaker in cases of subclinical hypothyroidism or hypothyroxinemia in pregnancy (7, 24, 25, 26). We found that LT-4 dose increased, as expected, during pregnancy, in this cohort of women with CH, and that more than two thirds of the TSH measurements reported during pregnancy indicated adequate control of thyroid function. However, the relatively small number of women with uncontrolled thyroid function described here (either with serum TSH concentration slightly above the upper limit of the reference range or overt hypothyroidism, suggesting non-optimal management or poor compliance with treatment), made it difficult to investigate the association of maternal thyroid dysfunction with the potential risk of adverse developmental milestones at one year in the offspring more fully. Thyroid function was not assessed during pregnancy in some of the patients and was assessed at different time points during pregnancy in the patients investigated. The normal or high serum TSH concentrations during pregnancy reported here may have been transient and not representative of TH availability during the crucial first trimester or first half of gestation or throughout pregnancy. We cannot, therefore, exclude the possibility that some of the women received inadequate treatment throughout pregnancy. This factor may be particularly important, given that inadequate treatment, resulting in subclinical or overt hypothyroidism, may affect pregnancy outcomes and the neurodevelopmental outcomes of the offspring (2, 5, 20, 21, 22, 23, 26). Further studies are therefore required, to determine whether thyroid function during pregnancy affects the

developmental milestones, at the age of one year, of the offspring of women managed and treated early for CH, to assess the time-dependent effects of maternal thyroid function on the neurodevelopmental outcome of the child and to determine whether the congenital nature of the mother's disease plays a role.

The strengths of our study include the population-based design of the cohorts, the large number of women with CH included, the exhaustive national coverage, the comparative design with an appropriate control group and the control for multiple confounding factors in both populations. Moreover, our analysis of this sample provides the first information about the recurrence of CH in the offspring of mothers with CH since the introduction of screening programs. Only one of the children was found to have CH, due to athyreosis; this child was born to a mother with an ectopic thyroid gland. This finding suggests that the risk of giving birth to a child with CH is no higher than expected from our previous report. Indeed, we previously showed that 2% of CH patients with abnormal thyroid development have a positive familial history and that ectopic thyroid gland may also occur in families affected by athyreosis, confirming the continuum of abnormalities in thyroid development (27, 28). Moreover, contrary to reports for the CH population (28), no significant numbers of extrathyroidal congenital malformation were reported in the offspring of this sample.

However, our study also had several limitations. The control group included only subjects born in north-eastern or central France, with a slightly higher level of education than for the national population (9), whereas the children born to mothers with CH belonged to a nationwide cohort (6). Despite the well-known risk of a lower educational level already reported for this population with CH (8), we cannot, therefore, entirely exclude the possibility of residual confounding bias due to the higher educational level of the reference population. Given the observational nature of data collection, we cannot exclude the possibility that some of the mothers with CH incorrectly gave negative (or positive) responses to certain questions, potentially leading to an underestimation (overestimation) of the number of observed milestones. However, this limitation is unlikely to apply, as we asked several questions for each domain and estimated a score from the answers to all questions within each domain, as in the reference population. Nevertheless, the information for each domain and the use of a self-reported questionnaire may also have resulted in misclassification. We used similar questionnaires in both populations, but,

for the reference population, the questions were asked by a midwife rather than directly answered by the mothers, for three domains: language, coordination and motor ability. Reporting bias cannot be excluded, but is unlikely to have been systematic and differential, because differences were observed only for the coordination domain (11). Another potential limitation of this study is that, despite the exclusion of reported thyroid diseases from the reference population, no data were available for iodine status, which may affect brain development in the child (5, 29). This study was performed in a population with proven iodine sufficiency, but iodine-deficient women and women with high iodine intake may have been present in the study populations (30), with potential effects on the association between thyroid function during pregnancy and neurodevelopmental outcome in the child.

In conclusion, the results of this observational study suggest that maternal CH may have mild adverse effects on some of the developmental milestones of the child at one year of age. The clinical implications are limited, but the observed difference suggest that the control of thyroid function during pregnancy may be an important determinant of early neurodevelopment. Further studies are required to confirm these findings and to investigate cognitive function in the longer term, with a view to determining whether subtle disadvantages persist during childhood in the children born to mothers with CH.

Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-17-0855>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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