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Maternal concentrations of human chorionic gonadotropin (hCG) and risk for cerebral palsy (CP) in the child. A case control study

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ABSTRACT

Background: Intrauterine conditions may be important in the development of cerebral palsy in the child. The hormone, human chorionic gonadotropin (hCG), is synthesized in the placenta, and hCG plays an important role in placental angiogenesis and development. Thus, maternal hCG concentrations may be an indicator of placental function and thereby the intrauterine environment for the offspring. We studied the associations of maternal concentrations of hCG during pregnancy with cerebral palsy in the child.
Methods: We performed a case-control study nested within a cohort of 29,948 pregnancies in Norway during 1992–1994. Cases were all women within the cohort who gave birth to a singleton child with cerebral palsy diagnosed before five years of age (n = 63). Controls were a random sample of women with a singleton child without cerebral palsy (n = 182).
Results: The adjusted odds ratio (OR) for cerebral palsyin the child was 0.78 (95% CI: 0.55–1.10) per log-transformed unit of maternal hCG in the 1 st trimester, and the OR was 1.42 (95% CI: 0.94–2.16) in the 2nd trimester. Thus, women who did not have high hCG concentrations in the 1 st trimester and low hCG concentrations in the 2nd trimester, had increased risk for giving birth to a child with cerebral palsy. Adjustments were made for pregnancy week of serum sampling, maternal age and parity.
Conclusions: The abnormal hCG concentrations in pregnancies with cerebral palsy in the offspring, could suggest placental factors as causes of cerebral palsy.

Introduction

Cerebral palsy (CP) is diagnosed in 2–3 per 1000 live born children in developed countries [1,2]. The diagnosis of CP is based solely on clinical symptoms. It is a disorder of movement and posture that limits activity, and the disorder is attributed to disturbances in the fetal or infant brain [3]. Previously, perinatal hypoxia was considered the major cause of CP, but recent studies suggest that prenatal causes are more important [2,4]. For example, preeclampsia [5] and high maternal body mass index [6] have been associated with increased risk of CP in the child. CP has also been associated with low birthweight [7], and with both high and low placental weight relative to birthweight [8]. These previous findings suggest that adverse intrauterine conditions influence the development of CP.

A well-functioning placenta is a determinant of fetal well-being. The hormone human chorionic gonadotropin (hCG) regulates embryo implantation and is important for growth and development of the placenta [9,10]. Therefore, deviance from normal hCG concentrations could indicate abnormal placental function.

HCG may be detected in maternal blood shortly after implantation of the embryo. In pregnancy, hCG is synthesized in trophoblastic cells only. In a normal pregnancy, a rapid increase in maternal hCG concentrations is seen during the first trimester, followed by a decrease in concentrations in the second trimester [11]. Low maternal hCG concentrations in early pregnancy have previously been associated with preeclampsia [11], advanced maternal age [12] and high maternal body mass index [13]. All these factors have also been associated with cerebral palsy in the child [5,6,14]. Hence, it is plausible that low hCG concentrations in early pregnancy are associated with CP in the offspring.

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In a case-control study nested within a cohort of 29 948 pregnancies, we studied the association of maternal hCG concentrations during pregnancy with the risk of CP in the child.

Material and methods

Design and data sources

We performed a case-control study nested within a population based cohort by linking the following Norwegian health registries; The Toxoplasmosis Study Biobank [15], the Medical Birth Registry of Norway [16] and the Registry of Cerebral Palsy in Children born 1986-95 [17]. These registries were linked by use of the unique person identification number given to all individuals living in Norway.

Between June 1992 and May 1994, almost all pregnant women in eleven out of nineteen counties in Norway (n = 35,940) participated in a prospective study of *Toxoplasma gondii* infection in pregnancy [15]. Of these, 200 women did not consent to the use of stored serum for future reseach, and 5212 women were not included in this study because their contact information was not available for obtaining consent (Fig. 1). Hence, 29,948 pregnancies and their offspring represent the source population for our study. The Toxoplasmosis Study Biobank has previously been used to study risk factors for preeclampsia [11], fetal growth restriction [18] and fetal death [19].

Information about CP in the child was obtained through linkage of the Toxoplasmosis Study with The Norwegian Registry of Cerebral Palsy in Children born 1986–95 [17]. This CP registry was established on the basis of discharge diagnoses during the years 1988–2001, at all hospitals with a pediatric department and at all child habilitation units in Norway. Hence, all children in the Toxoplasmosis Study could be identified, if CP had been diagnosed at the age of five or before. CP war diagnosed by a pediatrician specially trained in child neurology. The diagnosis of CP in our study, either as a primary or secondary diagnosis, was classified according to International Classification of Diseases (ICD)-9 (343.0-3 and 8–9) or ICD-10 (G.80.0-9) codes. Children whose CP was attributed to a postnatal cause (e.g. cerebral hemorrhage or infection) were excluded. Norway has public health care free of charge for children 16 years old or younger. Thus, it is assumed that virtually all children in Norway, who were born during 1986-95 and had been diagnosed with CP, were identified and included in the CP registry.

Study sample

Among the 29 948 pregnancies in the Toxoplasmosis Study, we identified by linkage to the CP registry a total of 78 children who had been diagnosed with CP before the age of five years (2.6 per 1000) (Fig. 1). All children with CP had been diagnosed after the age of one.

As controls, we randomly selected, within the Toxoplasmosis Study, 199 pregnancies without CP in the child. Children were eligible as controls if they had survived the first year after birth since the diagnosis of CP seldom is made before the age of one. The mean age at diagnosis for children with CP is known to be between 18 and 24 months [20,21]. Information about fetal death and infant death was obtained by linkage to the Medical Birth Registry of Norway [16]. This registry routinely obtains information about infant death from the Cause of Death Registry, Statistics Norway [22].

Only singleton born children were eligible for our study, since both hCG concentrations and the risk of CP vary by plurality. Thus, from the sample of 78 CP cases and 199 controls, we excluded fifteen multiple pregnancies (6 cases and 9 controls). We also excluded two control pregnancies with a child who did not reach the age of one year (fetal death or infant death), 10 pregnancies with missing information about parity (7 cases and 3 controls), and five pregnancies without any available serum samples for hCG quantification (2 cases and 3 controls) (Fig. 1). Thus, a total of 63 cases and 182 controls could be included in our study sample. In additional data analyses, we included only pregnancies with serum samples from both the first and the second trimester; 30 cases and 97 controls. In total, 32% of the children with CP, and 7% of the children without CP were born before pregnancy week 37.

Serum measurements

For all women in the Toxoplasmosis Study, the first blood sample was drawn in the 1 st trimester of pregnancy (median 9th week, range 4^{th}–12th week) [15]. In women without antibodies against *Toxoplasma gondii* in the first blood sample (90% of the women), additional blood samples were drawn in the 2nd (median 22nd week of pregnancy, range 13^{th}–27th week) and 3rd trimester (median 38th week of pregnancy, range 28^{th}–40th week). The serum samples were stored at $-20\,^{\circ}C$.

HCG concentrations were measured at the Department of Medical Biochemistry, St. Olav's Hospital, Trondheim, Norway, using an electrochemiluminescence immunoassay (ELISA) from Roche Diagnostics (Roche Diagnostics, Mannheim, Germany).

Statistical analyses

We compared mean maternal hCG concentrations (in international units per liter, (IU/L)) between cases and controls for each trimester of pregnancy. Differences were tested by Student's t-test.

We used logistic regression analyses to study the associations (odds ratios (OR) with 95% confidence intervals (CI)) of maternal hCG concentrations with CP in the offspring. In these data analyses, hCG concentrations were log-transformed since the concentrations were not normally distributed [13]. The associations were analyzed for each trimester, and we made adjustment for pregnancy week at serum sampling, maternal age (<30 or ≥ 30 years) and parity (0 or ≥ 1 previous deliveries after 16 weeks of pregnancy). These factors have been associated with maternal hCG concentrations and/or CP [11,12,14].

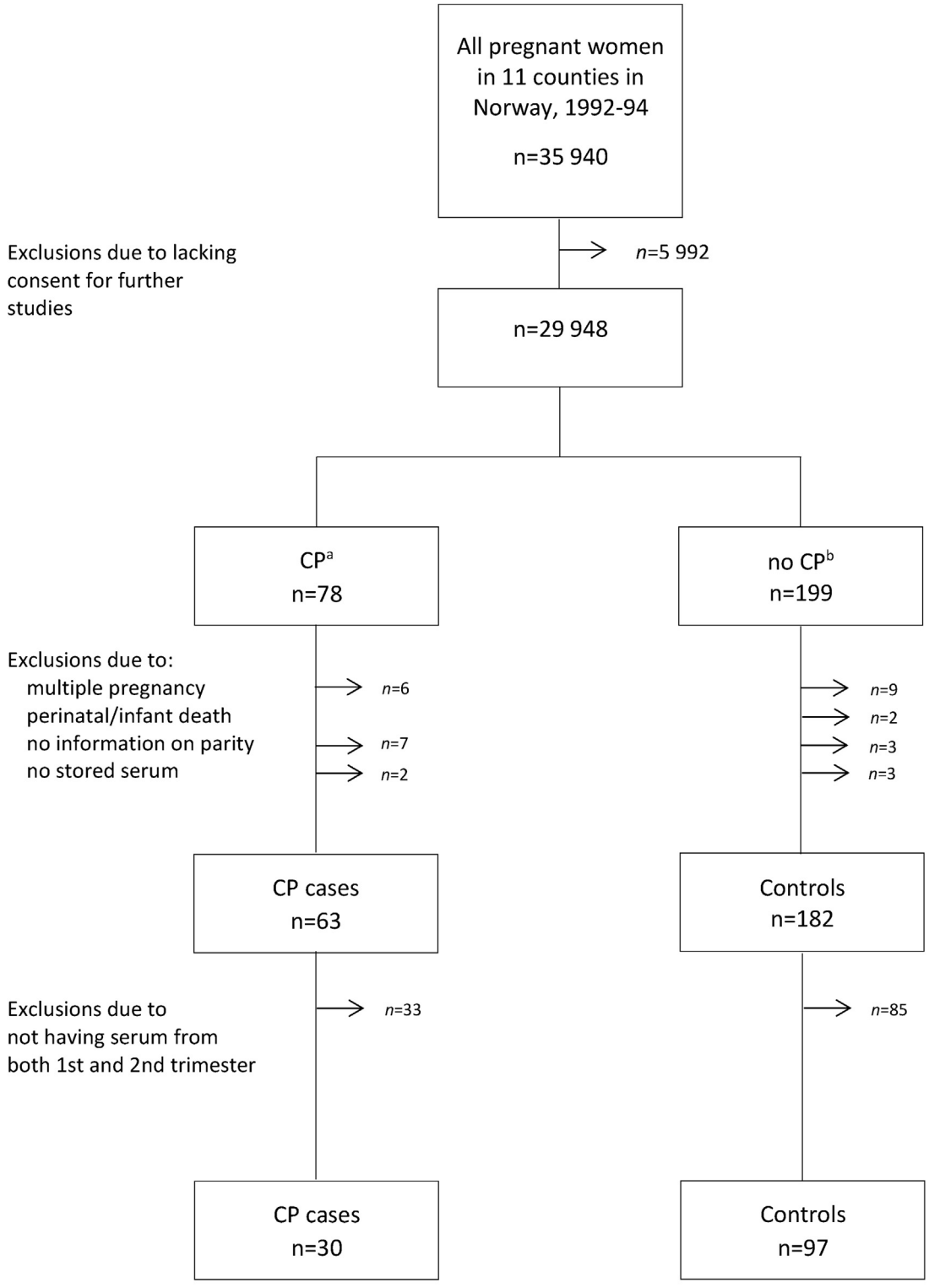
We also estimated the associations of CP in the child with changes in maternal hCG concentrations from the 1 st trimester to the 2nd trimester. In these analyses, crude hCG concentrations from control women were divided at the median, and "low hCG concentrations" represent concentrations below median, and "high hCG concentrations" represent concentrations above the median in the index trimester. Pregnancies with "high" hCG concentrations in 1rst trimester and "low" hCG concentrations in the 2nd trimester (normal changes in hCG concentrations) were used as the reference group.

Our study was approved by the Norwegian Data Inspectorate (reference number 2000/1431-2) and Regional Committee for Medical Research Ethics (reference number S-99106).

Results

Mean duration of pregnancy was 37.1 weeks for cases and 39.7 weeks for controls. Table 1 shows the distributions of study factors in each trimester. Since not all women had a serum sample from each trimester available, the number of pregnancies in each trimester varied.

In the 1 st trimester, mean maternal hCG concentration were lower in cases than in controls (8226 versus 94,510 IU/L, p = 0. 23, Student's t-test) (Table 1, Fig. 2). In the 2nd and in the 3rd trimester the differences were in the opposite direction, and cases had



[a]All children with CP; [b]Drawn at random among children without CP

Fig. 1. Flow chart of the study sample.

Table 1
Characteristics of the study sample by trimester of pregnancy.

	CP cases	Controls	*p*-value	All pregnancies
1 st trimester				
N	43	126		169
Mean hCG (SD)	82 261 (55,685)	94 510 (63,948)	0.23	91 393 (62,020)
Week of hCG measurement, mean (SD)	8.91 (1.86)	8.86 (2.12)	0.88	8.87 (2.05)
Maternal age ≥30 years (%)[range, years]	33 [20–43]	32 [18–41]	0.92	32 [18–43]
First time mother (%)	60	49	0.20	52
2nd trimester				
N	56	180		236
Mean hCG (SD)	32 500 (29,771)	28 994 (29,864)	0.44	29 826 (29,816)
Week of hCG measurement, mean (SD)	20.70 (3.95)	20.62 (3.99)	0.90	20.64 (3.97)
Maternal age ≥30 years (%) [range, years]	36 [20–43]	42 [18–41]	0.38	41 [18–43]
First time mother (%)	64	43	0.01	48
3nd trimester				
N	40	142		182
Mean hCG (SD)	30 031 (29,533)	25 287 (24,598)	0.36	26 329 (25,752)
Week of hCG measurement, mean (SD)	36.58 (3.28)	37.14 (2.50)	0.32	36.02 (2.69)
Maternal age ≥30 years (%) [range, years]	28 [20–43]	39 [18–41]	0.15	37 [18–43]
First time mother (%)	73	45	p < 0.01	51

CP cases, pregnancies with cerebral palsy in the offspring.
hCG, maternal human chorionic gonadotropin concentrations in liters per international units (l/IU).
SD, standard deviation.
p-value is for differences in measures between cases and controls, applying two-sided Student's *t*-tests.

higher mean hCG concentrations than controls. The differences in mean hCG concentrations between cases and controls did not reach statistical significance in any of the trimesters (Table 1).

The adjusted OR for CP in the child was 0.78 (95% CI 0.55–1.10) per log-transformed unit of maternal hCG in the 1 st trimester (Table 2). In the 2nd trimester, high hCG concentrations were associated with increased risk of CP, and the adjusted OR per log-transformed unit of hCG was 1.42 (95% CI: 0.94–2.16).

For a total of 127 women (30 cases and 97 controls), hCG had been quantified in both 1 st and 2nd trimester, and in this subsample associations of individual changes in hCG concentrations with risk for CP could be studied. Thus, compared to women with high hCG concentrations in the 1 st trimester (above the median among controls) and low hCG concentrations in 2nd trimester (below the median among controls), women with other patterns of change (low/ high, low/low, high/high) had higher estimated OR for CP in the child (Table 3). Women with low hCG concentrations (below the median) in both 1 st and 2nd trimester, had the highest estimated risk for CP in the child adjusted OR 2.75 (95% CI; 0.84–9.04).

Discussion

Our findings suggest that abnormal maternal hCG concentrations during pregnancy are assocatied with increased risk for CP in the child. Since hCG is synetized in the placenta and is involved

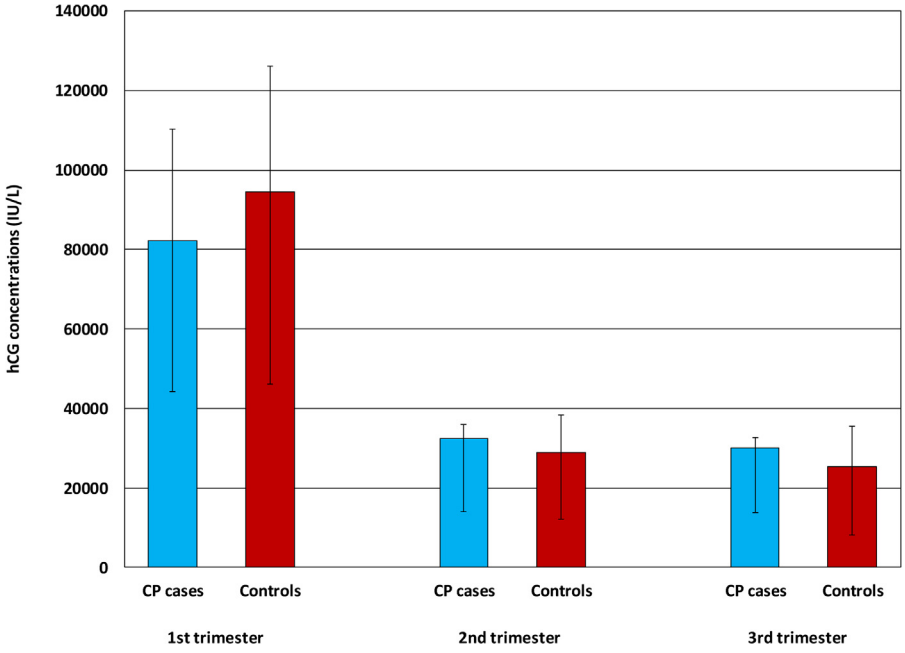


Fig. 2. Mean hCG concentrations, in international units per liter (IU/L), in pregnancies with (cases) and pregnancies without cerebral palsy (CP) in the child (controls) for each trimester of pregnancy.

Table 2
Crude and adjusted odds ratios (OR) for developing CP in the child according to maternal hCG concentrations (log transformed) in 1 st, 2nd and 3rd trimester of pregnancy. Adjustments are made for pregnancy week of hCG measurement, maternal age[a] and parity[b].

	Crude		Adjustment for pregnancy week of hCG measurement only		Additional adjustment for mother's age and parity	
	OR	95% CI	OR	95% CI	OR	95% CI
1 st trimester (n = 169):						
hCG (log)	0.80	(0.58–1.11)	0.77	(0.55–1.10)	0.78	(0.55–1.10)
2nd trimester (n = 236):						
hCG (log)	1.30	(0.95–1.79)	1.53**	(1.02–2.28)	1.42*	(0.94–2.16)
3rd trimester (N = 182):						
hCG (log)	1.07	(0.83–1.37)	1.05	(0.81–1.35)	1.01	(0.80–1.26)

* $p < 0.10$.
** $p < 0.05$.
[a] Maternal age <30 years is the reference category.
[b] Parity ≥1 is the reference category.

Table 3
Odds ratios for developing CP in the child by changes in maternal hCG concentrations from the 1 st to the 2nd trimester of pregnancy, among 30 pregnancies with CP in the child and 97 controls.

	Mean hCG concentrations 1 st and 2nd trimester	Adjustment is made for week of hCG measurement		Additional adjustments for mother's age[b] and parity[b]	
		OR	95% CI	OR	95% CI
$high_{1st}$-low_{2nd}[c]	141 951–12 296	1.0		1.0	
low_{1st}-low_{nd}	50 439–10 368	2.18	(0.68–6.96)	2.75*	(0.84–9.04)
low_{1st}-$high_{nd}$	39 660–33 433	1.87	(0.51–6.98)	1.74	(0.46–6.57)
$high_{1st}$-$high_{nd}$	151 650–37 747	1.59	(0.42–6.02)	1.73	(0.45–6.74)

High hCG concentrations refer to above, and low hCG concentrations refer to below median concentrations among controls in the i ndex trimester.
*$p < 0.10$.
[a]Mother's age <30 years is reference category.
[b]Parity ≥1 is reference category.
[c]hCG concentrations in the 1 st trimester and in the 2nd trimester.

in the relulation of growth and angiogenseis in pregnancy, our findings suggest that placental factors may contribute to the development of CP.

Limitations of findings

Our study was population-based, and in the source population almost 100% of all pregnant women in eleven out 19 counties in Norway participated. Among the 29,948 pregnancies in the source population, we idenfied 78 childeren diagnosed with CP. This prevalence is similar to the CP prevalence in the general population of children in Norway during our study period [1]. Therefore, we believe that almost all children diagnosed with CP in our cohort were identified and included as cases in our study. Our controls were randomly selected among pregnancies with offspring without a diagnosis of CP at the age of five. In total, we believe that selection bias is unlikely in our study.

CP is a rare disorder, and despite our large cohort, few children developed CP. We had therefore limited statistical power. In particular, we could not study the association of hCG concentrations with CP sub-types, or within birthweight or gestational age groups. Also, the small number of CP cases combined with the small number of women with very low hCG concentrations in the 1 st trimester, precluded a targeted analysis of these women.

The sera were stored for almost 20 years before hCG was quantified. To ensure comparable measurements in cases and controls, all sera should have been analyzed at the same time, but the sera from CP cases were analysed two years later than the sera from the controls. Although serum storage and analyses were the same in all other aspects, and the difference in serum storage time was less than 10%, we cannot rule out that differences in storage time between cases and controls may have influenced the measurements. However, the differences in changes in hCG concentrations from the 1 st to 2nd trimester between cases and controls, cannot be explained by delayed serum analyses in CP cases.

In a normal pregnany, maternal hCG concentrations vary largely by gestational age [11]. In our study, there was little difference in pregnancy week of serum sampling between cases and controls, and adjustments for week of serum sampling did not change our estimates notably. Also, our estimates remained almost unchanged after adjustment for parity and maternal age. We had no information about materal body mass index in this study. High maternal body mass index has been associatad with CP in the child [6], and also with low maternal hCG concetrations in early pregnancy [13]. High maternal body mass index could therfore be an underlying explanation for the association of abnormal maternal hCG concetrations with offspring CP in our study.

High maternal hCG concentrations in the 1 st trimester have been linked to chromosomal abnormalities in the child [23]. If chromosomal abnormalities are more prevalent among our CP cases than among controls, our estimates of low hCG concentrations with CP risk may represent underestimates. However, no cases nor controls within our study were reported with Down'-syndrome to the Medical Birth Registry of Norway (data not shown).

Being born preterm increases the risk for CP [24]. Low hCG concentrations in early pregnancy have been associated with increased risk for miscarriage 1 st trimester [25]. In pregnancies that last beyond the 1 st trimester, low hCG concetrations in early pregnancy have been associated with longer duration of pregnancy [26]. Thus, low hCG concentrations in 1 st trimester is not likely to be a marker of preterm delivery, and thereby increased risk of CP in the child.

Interpretations of findings

Our findings suggest that abnormal maternal hCG concentrations are associated with increased risk for CP in the child.

HCG is an important angiogenic factor in pregnancy, and regulates the development of placental vessels in interplay with other angiogenic factors [9,10]. We are aware of no previous studies of maternal hCG concentrations, or any other angiogenic factors, with susequent risk for CP in the child. However, known maternal risk factors for CP have been associated with abnormal hCG concentrations, such as preeclampisa [11], and high maternal body mass index [13]. Also, angiogenic factors other than hCG have been associated with risk factors for CP such as, preeclampsia [27] and low birthweight [18].

Abnormal hCG concentations may be an indicator of feto-placental hypoxia. HCG is synthesized by trophoblast cells in the placenta, and is known to stimulate trophoblast proliferation [9,10,28]. Thus, low hCG concentrations in the 1 st trimester could indicate slow proliferation of trophoblast cells and thereby slow or impaired development of the placenta. A small placenta has previously been associated with CP in the offspring [8], and a small placenta may indicate suboptimal oxygen supply to the growing fetus.

Increased angiogesis is a known response to hypoxia [29]. Thus, the relatively high hCG concentrations in the 2nd and 3rd trimester in CP cases, could possibly represent an angiogenic reponse to feto-placental hypoxia. Interestingly, the highest risk for CP in the child was observed in pregnancies with low hCG contentrations in both 1 st and 2nd trimester. This finding could possibly suggest that pregnancies with impared placental delvelopment in the first trimester and with no or little subesquent angiogenic response, have the highest risk for CP in the child.

In conclusion, our findings suggest that abnormal maternal hCG concetrations during pregnancy are associated with increased risk for CP in the child. These findings may indicate that impaired early placental development and thereby insufficient oxygen supply to the growing fetus may be an undelying cause of CP.

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