Maternal H. pylori seropositivity is associated with gestational hypertension but irrelevant to fetal growth and development in early childhood

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Abstract

Background: Helicobacter pylori infection is known to alter growth-related hormones and cause growth faltering in young children. It is still unknown if maternal H. pylori infection has an impact on the levels of cord blood growth-related hormones and can predict intrauterine growth restriction and poor physical and neurodevelopmental outcomes in children. This study aimed to examine the associations between maternal H. pylori infection and pregnancy-related adverse events, fetal growth and early childhood development.

Methods: The prospective cohort study recruited singleton pregnant women without major medical illnesses from January 2014 to January 2015. Seropositivity for H. pylori was defined by >12 U/ml of anti- H. pylori IgG in the maternal serum. Demographic data and pregnancy-related medical issues of the cohort were documented. Cord blood levels of insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), insulin, and ghrelin were determined using ELISA test. The growth of eligible neonates was monitored annually for up to 3 years, and cognitive development was assessed using the comprehensive developmental inventory for infants and toddlers (CDIIT) test 3 years after birth.

Results: Of the 106 enrolled women, 25 (23.6%) were H. pylori -seropositive. Maternal H. pylori seropositivity was correlated with a higher risk of developing gestational hypertension (GH) (12% vs. 1.2%, p =0.04) and lower cord blood levels of IGF-1 (<35 ng/ml, 70.0% vs. 40.7%, p =0.02) and IGFBP-3 (<1120 ng/ml, 100.0% vs. 76.3%, p =0.02) compared with the seronegative women. No significant impact on birth weight, childhood growth and cognitive development was found to correlate with maternal H. pylori seropositivity during pregnancy.

Conclusions: Maternal H. pylori infection during pregnancy was more likely to develop GH, but not correlated with fetal and childhood growth and development. In addition to close monitoring of hypertension, H. pylori eradication can be considered for such H. pylori -infected mothers.

Background

Helicobacter pylori infects more than half of the global population, although its prevalence varies widely among different countries. Low socioeconomic status and poor sanitary or hygienic conditions are thought to correlate with the prevalence of *H. pylori* infections. Primary *H. pylori* infections occur most commonly in early childhood. The reported annual spontaneous seroreversion rates range from 1% to 2% both in children and adults [1, 2]. Although it seldom causes clinical symptoms in children, chronic *H. pylori* infection can pose serious health threats. Indeed, the bacterium is known to promote the development of chronic gastritis, peptic ulcer diseases, MALT lymphoma and gastric cancer in 10% of the infected population. Furthermore, there is growing evidence, mainly obtained from observational studies, showing that *H. pylori* infection may impair growth in children [3–5]. Indeed, *H. pylori*-inducedchronic gastritis results in the loss of appetite, malabsorption of nutrients, and dysregulation of the gastric endocrine and growth hormone systems, all of which may contribute to childhood growth impairment [6].

Notably, we previously showed that the successful eradication of *H. pylori* restores systemic ghrelin levels and improves growth in children [7].

H. pylori infection during pregnancy is related to several adverse outcomes in both mothers and neonates [8, 9]. Two cohort studies conducted in Uganda and Sudan demonstrated that maternal *H. pylori* infection was correlated with low birth weight in neonates [10, 11]. However, this effect was not observed in mouse models [12]. Another prospective cohort study conducted in the Netherlands identified *H. pylori* infection as an independent risk factor for frequent vomiting during pregnancy, and that this was correlated with an increase in small for gestational age (SGA) neonates [8]. Moreover, a separate case-control study revealed that a significantly higher percentage of women positive for *H. pylori* stool antigen (HPSA) (indicative of *H. pylori* infection) developed preeclampsia (PE) with intrauterine growth restriction (IUGR) compared with HPSA-negative women. It is thought that *H. pylori*-inducediron deficiency anemia (IDA) plays a role in driving IUGR as well [13, 14]. These results thus indicated possible etiopathological connections between maternal *H. pylori* infection and IUGR. It has been previously documented that cord blood levels of insulin, insulin-like growth factors (IGFs), insulin-like growth factors binding proteins (IGFBPs), and ghrelin are correlated with intrauterine fetal growth [15–18]. However, no previous study has addressed the role of these growth factors and hormones in maternal *H. pylori* infection and IUGR.

Children born as SGA are associated with poor neurodevelopmental outcomes [19–21]. Similarly, *H. pylori* infection has been negatively correlated with cognitive development in children of early school age [22].Interestingly, intraperitoneal injections of *H. pylori* filtrate have been shown to be sufficient to induce spatial learning and memory deficit in rats [23]. However, it is currently unclear whether maternal *H. pylori* infection negatively impacts on the neurodevelopment potential of the fetus. In this prospective cohort study, we investigated the effects of maternal *H. pylori* infection and related pregnancy disorders on growth and development of the fetus, neonates and during early childhood.

Methods

Subject recruitment and follow-up

Singleton pregnant women who attended regular antenatal examinations at one obstetric-pediatric clinic in Tainan City, Taiwan, between January 2014 and January 2015 were identified and recruited into the study. Eligibility was then assessed between 28 and 32 weeks of gestation. Individuals with underlying medical conditions such as chronic hypertension, pre-gestational diabetes mellitus, chronic lung disease, renal disease, major cardiac disease, autoimmune conditions, thyroid disease, malignancy, and uterine malformations were excluded. Individuals that had a history of illicit drug abuse and those whose fetuses had chromosomal abnormalities, congenital malformations or evident congenital infections (TORCH) were also excluded. Follow-up assessments were carried out at the time of delivery, and at 1, 2, and 3 years after delivery.

This study was approved by the Ethics Committee (B-BR102–001) of National Cheng Kung University Hospital, Tainan, Taiwan. Written informed consent was obtained from each participant and her spouse. The demographic characteristics, anthropometric data, and common risk factors of SGA were collected and assessed. These included maternal age, body height, body weight before pregnancy, body mass index (BMI) before pregnancy, habits of cigarette smoking, alcohol use, maternal educational attainment, annual household income, and pregnancy complications such as antepartum bleeding, anemia, pregnancy-induced hypertension (PIH), and PE. Anemia was defined by a hemoglobin concentration of less than 11 g/dL. PIH was defined by any new onset of hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) after 20 weeks of gestation. PE was defined by the combination of PIH and proteinuria or signs of end-organ dysfunction.

The corresponding neonates enrolled in the follow-up were full-term (gestational age 37–40 weeks) and healthy. Parameters recorded at birth included gestational age, body weight and length at birth, head circumference at birth, and Apgar score at 1 and 5 minutes post-delivery. Neonates that required post-delivery intensive care were excluded from the follow-up study.

Maternal serum collection and testing for anti-*H. pylori* IgG

The status of *H. pylori* infection was examined by measuring serum IgG against *H. pylori* using a commercial *H. pylori* IgG ELISA kit (IBL, Hamburg, Germany) at 28–32 weeks of gestation, the period when a routine screening test for hepatitis B surface antigen is commonly conducted in Taiwan. Anti-*H. pylori* IgG titers above 12 U/ml were considered positive, while titers below 8 U/ml were considered negative. Titer values between 8 and 12 U/ml were considered equivocal. The cohort of mothers were subsequently categorized as either *H. pylori*-seropositive or *H. pylori*-seronegative according to the ELISA results.

Cord blood levels of IGF–1, IGFBP–3, insulin, and ghrelin

Cord venous blood samples were collected at delivery and centrifuged at 3500 x g for 30 minutes at 4°C to separate the serum. The serum samples were stored at –80°C. IGF-I (R&D Systems, Inc. Minneapolis, MN, USA), IGFBP–3 (R&D Systems, Inc. Minneapolis, MN, USA), insulin ((R&D Systems, Inc. Minneapolis, MN, USA) and ghrelin (EMD Millipore Corporation, St. Charles, MO, USA) levels were measured using ELISA following the manufacturers' instructions.

Assessment of anthropometric parameters and cognitive development of newborns

The enrolled newborns were studied longitudinally for up to 3 years of age. The weight and length of each child were measured at birth and then annually. According to the gestational age of infants born in

Taiwan, SGA was defined by a birth weight below the 10^{th} percentile [24].

Cognitive development in young children was assessed using the comprehensive developmental inventory for infants and toddlers (CDIIT) test at 3 years of age. The CDIIT is a reliable pediatric norm-referenced assessment that is widely used for the clinical diagnosis of developmental delays in five major developmental areas. These include cognition, language, motor, social and self-care skills [25, 26]. The CDIIT test consists of a diagnostic test (CDIIT-DT) and a screening test (CDIIT-ST). In this study, we applied the cognition subtest of the CDIIT-DT and assessed five aspects of a child's mental capacity, including attention, perception, memory, reasoning and concepts of color, shape, size, and number. The evaluations were conducted by a trained administrator.

H. pylori stool antigen test (HPSA) and definition of *H. pylori* infection in children

Stool samples were collected from the enrolled young children at 1, 2 and 3 years after birth to detect new *H. pylori* infections using the HPSA test. The HPSA test (Meridian Diagnostic Inc., Cincinnati, Ohio, USA) utilized a plurality of monoclonal anti-*H. pylori* antibodies adsorbed to microwells. The results were interpreted spectrophotometrically, and the cutoff optical density at 450 nm for a positive outcome was set at 0.14. Children with a positive HPSA test in any one of the three samples were considered to be infected with *H. pylori,* while those who showed negative HPSA test following a previous positive result were defined as spontaneous elimination of *H. pylori* infection. A minimum of two consecutive positive HPSA tests that lasted until the end of the study was considered to indicate persistent *H. pylori* infection. Children with negative HPSA tests throughout the follow-up period were considered to be non-infected.

Statistical analysis

Demographic data and measurable parameters were presented as frequencies and mean ± standard deviation (SD). Significance of association was determined using the Pearson chi-square ($\chi 2$) test for categorical variables and independent sample *t*-test for continuous variables. As ELISA tests tend to produce high standard deviation values which may give rise to type II statistical errors, receiver operating characteristic (ROC) curve analysis in conjunction with Youden's index was used to determine the best cutoff values of cord blood IGF−1, IGFBP−3, insulin and ghrelin levels to differentiate *H. pylori*-seropositive and *H. pylori*-seronegative mothers. A *p* value of less than 0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS Statistics V.17.0.

Results

Study design and enrolled subjects

Fig. 1 show the workflow of the study and the data collected. A total of 108 singleton pregnant women were initially recruited. Two participants were eventually excluded due to chronic hypertension and thyroid disease. The sera of the remaining 106 participants were collected and tested for anti-*H. pylori* IgG as specified. A total of 79 cord blood samples were analyzed for IGF−1, IGFBP−3, insulin, and ghrelin levels. For the follow-up assessments, five preterm newborns (gestational age <37 weeks) and one who was lost to follow-up were removed from the cohort.

Seropositivity and clinical characteristics of the voluntary mothers

Our results showed that 25 (23.6%) out of the 106 pregnant women were positive for serum anti-*H. pylori* IgG (*Table 1)*.. However, no significant distinctions in the age, pre-pregnancy body weight, height, BMI, household size, annual household incomes, educational attainment, job, smoking habits, alcohol drinking habits, hemoglobin, and placental weight were found between these two groups ($p > 0.05$). A significantly higher incidence rate of PIH was observed in the *H. pylori*-seropositive mothers than in the seronegative mothers (12% vs 1.2%, $p < 0.05$). Moreover, the cord blood IGF−1 and IGFBP−3 levels were modestly lower in the *H. pylori*-seropositive group compared with the seronegative group. According to our ROC curve analysis and Youden's index, *H. pylori*-seropositive mothers were significantly more likely to have a cord blood IGF−1 level below 35 ng/ml (70.0% vs 40.7%, $p = 0.023$) and IGFBP−3 level below 1250 ng/ml (100% vs 76.3%, $p = 0.02$) compared with seronegative mothers (*Table 2)*..

The association of maternal *H. pylori* seropositivity and birth weight, early childhood growth, and cognitive development

Table 3 shows anthropometric data and the cognitive development in children of *H. pylori*-seropositive and seronegative mothers in the first 3 years after birth. No significant differences in body weight, length and head circumference at birth were observed between the *H. pylori*-seropositive group and the seronegative group. Likewise, the rates of SGA and low birth weight (LBW, birth body weight <2500 g) were similar in the two groups. The body weight and height subsequently measured at 1, 2, and 3 years after birth also revealed no significant difference between the children born to *H. pylori*-seropositive and seronegative mothers. Lastly, CDIIT assessments of children at the 3-year time point revealed no significant difference in the cognitive development between the two groups of children (*Table 3)*..

Susceptibility of *H. pylori* infection in the children during the follow-up period

Serial HPSA tests were performed in children at 1, 2, and 3 years after birth. Among the cohort of 58 children who received HPSA tests, none was infected with *H. pylori* in the first year. In the second year, two of 16 children (12.5%) from the *H. pylori*-seropositive group and one of 31 children (3.2%) from the *H. pylori*-seronegative group were found to be HPSA positive ($p = 0.26$). In the third year, one more child from the maternal *H. pylori*-seropositive group was found to be HSPA positive. However, one child that was previously HSPA positive became HPSA negative, while two children remained HSPA positive (persistent infection).

Analysis of risk factors of SGA in singleton term neonates

The risk factors for SGA were further evaluated *(Table 4)*.. No significant differences in maternal anthropometric and socio-demographic characteristics were found in the SGA group compared with the non-SGA group. However, the SGA neonates exhibited a significantly lower placental weight (445.0 vs 514.9 g, $p < 0.01$), lower cord blood IGF−1 levels (24.7 vs 40.1 ng/mL, $p = 0.04$) and higher ghrelin levels (1045.1 vs 782.3 pg/mL, $p < 0.01$) compared with the non-SGA group.

Discussion

This is the first 3-year prospective cohort study to evaluate the relevant implications of maternal *H. pylori* infection during pregnancy on fetal growth, as well as the growth and cognitive development in young children. Our results showed that *H. pylori*-seropositive individuals had higher risks of developing PIH during pregnancy. In addition, our results showed that the levels of the cord blood IGF−1 and IGFBP−3 were lower of *H. pylori*-seropositive mothers compared with those of seronegative mothers, even though no apparent changes in birth weight and neonatal size were observed. Our results suggested that early childhood growth and cognitive development were not affected by maternal *H. pylori* infection during pregnancy.

In contrast to our observations, a previous study conducted by Eslick et al. reported that *H. pylori*-seropositive women were more likely to give birth to undersized neonates than seronegative women due to IUGR [27]. In a separate study conducted in Uganda, Wanyama et al. showed that maternal *H. pylori* infection was an independent predictor of low birth weight in newborns [10]. Likewise, Mustafa et al. demonstrated that maternal *H. pylori* seropositivity was more frequently associated with low birth weight [11]. However, these studies did not consider the effects of other potential confounding events that are commonly experienced during pregnancy, such as severe nausea, vomiting, PE, and anemia. We hypothesize that these factors could potentially explain the discrepant findings between previous studies and our current study.

Although not entirely understood, the mechanism by which maternal *H. pylori* infection impacts birth weight may be multifactorial. Maternal *H. pylori* infection has been reported to be a risk factor for hyperemesis gravidarum, PE, and IDA during pregnancy [8, 13, 28–30]. These events also contribute to SGA or IUGR. Interestingly, virulent factors of *H. pylori* have also been considered to be a cause of IUGR.

Similarly, previous studies have shown that persistent CagA/VacA-positive *H. pylori* infection in pregnant women caused PE and IUGR [31], and that SGAcorrelated specifically withinfections caused by CagA-positive strains of *H. pylori* [32]. Although the virulent factors of *H. pylori* from infected mothers were not tested in the current study, almost all strains of *H. pylori* isolated from Taiwanese patients are CagA/VacA-positive [33]. Notably, the rate of PIH was found to be higher in the *H. pylori*-seropositive group compared with the seronegative group. However, no significant correlations were observed for anemia or preeclampsia.

Since *H. pylori* infection has been reported to alter growth hormones [32], we investigated the effects of *H. pylori* infection on cord blood levels of IGF–1, IGFBP–3, insulin, and ghrelin, as well as the relationships between these hormones and IUGR. Consistent with previous studies which reported decreased levels of IGF–1, IGFBP–3, insulin, and increased levels of ghrelin in the cord blood of IUGR neonates [17, 34–36],our data showed significantly lower levels of IGF–1 and higher levels of ghrelin in the cord blood samples of SGA neonates compared with those of non-SGA neonates. Our results also revealed that maternal *H. pylori*-seropositivity during pregnancy was correlated with lower levels of IGF–1 and IGFBP–3 in the cord blood. However, of all the potential risk factors and parameters considered, only placental weight, but not PIH or *H. pylori*-seropositivity, was found to be associated with SGA.

Given all the evidence so far, it is likely that *H. pylori* infection during pregnancy causes SGA via indirect mechanisms such as the aforementioned adverse effects that are commonly associated with *H. pylori* infection. However, further studies are required to confirm this.

The data obtained in the current study indicated that there were no significant differences in early childhood growth and cognitive development between children born to *H. pylori*-seropositive mothers and seronegative mothers. In addition, maternal *H. pylori*-seropositivity during pregnancy did not increase the risk of acquiring *H. pylori* infection in children. This is consistent with our observations that maternal *H. pylori* infection status did not affect initial birth weight.

There are several limitations to this study. First, SGA was used as a surrogate for IUGR. However, this clinical definition does not distinguish between constitutionally and pathologically small fetuses [37, 38]. On the other hand, although suffering from intrauterine growth deceleration, IUGR infants may have appropriate birth weight as per gestation. “True” IUGR infants are mostly a consequence of placental insufficiency, and they present with poorer perinatal and long-term outcomes compared with constitutionally SGA neonates [38, 39]. Thus, ways to more effectively distinguish neonates with IUGR would be more clinically relevant. Second, not all risk factors of SGA were considered in this study. SGA risk factors such as maternal weight gain, nutritional status during pregnancy, PE and hyperemesis gravidarum prevalence and severity may also play important roles and should therefore be studied in the future. Indeed, maternal weight gain during pregnancy was positively correlated with neonatal birth weight [40]. Third, given that placental weight was negatively correlated with the risk of SGA [41, 42],we relied on placental weight as a representative of overall placental condition. However, more in-depth evaluations of specific placental parameters such as uterine artery velocimetry or expression of

biomarkers should be performed. This would allow important weight-independent physiological and pathological changes of the placenta to be detected more effectively. Furthermore, our serology *H. pylori* IgGtest, which was used to define infection status in our cohort, did not distinguish previously cleared infections from ongoing infections [43].Lastly, there were missing data during the 3-year follow-up period, which may have led to bias in the results.

Conclusions

In this prospective cohort study in Taiwan, we found that maternal *H. pylori* infection per se did not promote SGA in neonates. We showed that SGA was most likely caused by other *H. pylori*-induced pathologies and pregnancy-related complications such as hyperemesis gravidarum, PE, and anemia. Moreover, we revealed that maternal *H. pylori* infection did not directly impair growth and cognitive development in children during early childhood. However, as *H. pylori*-infected pregnant women are more likely to develop PIH, increased attention should be paid to prevent hypertension-related complications in these individuals. Future study can be promising to evaluate the possible mechanisms by which *H. pylori* directly affects PIH, or to assess whether *H. pylori* eradication can decrease such PIH risk for mothers.

Abbreviations

SGA: small for gestational age; HPSA: *H. pylori* stool antigen; PE: preeclampsia; IUGR: intrauterine growth restriction; IDA: iron deficiency anemia; IGFs: insulin-like growth factors; IGFBPs: insulin-like growth factors binding proteins; BMI: body mass index; GH: gestational hypertension; CDIIT: comprehensive developmental inventory for infants and toddlers.

Declarations

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The authors have no financial relationships relevant to this article to disclose.

Authors' contributions

FPL involved in the study design, study conduction, interpretation of data, and in drafting the manuscript. YFT contributed in the study design and in the interpretation of data. BSS involved in the study design

and conduction, interpretation of data, and editing the manuscript. YJY contributed in the setting of the study design and conduction, interpretation of data, editing and final approval of the manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the Ethics Committee (B-BR102–001) of National Cheng Kung University Hospital, Tainan, Taiwan. Written informed consent was obtained from each participant and her spouse.

Consent for publication

Not applicable.

Competing interests

The authors declare that there were no competing interests.

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Tables

Table 1. The characteristics of mothers in *H. pylori*-seropositive and seronegative groups.

Variable, mean ± SD or number (%)	Serum *H. pylori* IgG		*p* value
	Seropositive (n=25)	Seronegative (n=81)	
Maternal age (years)	31.0 ± 4.0	32.1 ± 3.8	0.20
Maternal body height (cm)	159.5 ± 5.5	159.9 ± 4.4	0.70
Maternal pre-pregnancy body weight (kg)	52.2 ± 5.9	55.5 ± 8.2	0.06
Maternal pre-pregnancy BMI (kg/m^2)	20.6 ± 2.5	21.7 ± 3.1	0.09
Household size (person)	3.8 ± 1.7	3.7 ± 1.8	0.69
Annual household income			0.79
Low[a]	7 (28.0)	25 (30.9)	
Middle/High	18 (72.0)	56 (69.1)	
Educational attainment			0.68
Low/Middle[b]	1 (4.0)	8 (11.1)	
High	24 (96.0)	73 (67.9)	
Housewife	5 (20.0)	25 (30.9)	0.45
Primigravida	18 (72.0)	48 (59.3)	0.25
Smoking	0 (0.0)	1 (1.2)	1.00
Alcohol	3 (12.0)	5 (6.2)	0.39
Gestational age (week)	38.5 ± 1.0	38.8 ± 1.1	0.26
Placental weight (g)	505.2 ± 65.3	508.5 ± 47.4	0.79
Hemoglobin (g/dL)	11.9 ± 1.7	11.9 ± 1.4	0.98
Pregnancy-induced hypertension	3 (12.0)	1 (1.2)	0.04
Preeclampsia	0 (0.0)	0 (0.0)	1.00
Bleeding at early gestation	0 (0.0)	2 (2.5)	1.00

[a]Annual household income <16,200 USD

[b]Educational attainment below bachelor level

Table 2. The association of cord blood IGF-1, IGFBP-3, ghrelin, insulin levels and maternal *H. pylori* seropositivity

Variable	Serum *H. pylori* IgG		*p* value
Number (%)	Seropositive (n=20)	Seronegative (n=59)	
IGF-1 < 35 (ng/ml)	14 (70.0)	24 (40.7)	0.02
IGFBP-3 < 1120 (ng/ml)	20 (100)	45 (76.3)	0.02
Insulin < 35 (pmol/l)	17 (85.0)	38 (64.4)	0.10
Ghrelin > 925 (pg/ml)	3 (15.0)	16 (27.1)	0.37

Table 3. The anthropometric characteristics and cognitive development of children by maternal *H. pylori* status.

Variable	Serum *H. pylori* IgG		*p* value
Mean ± SD or number (%)	Seropositive (n=23)	Seronegative (n=77)	
Birth body length (cm)	50.0 ± 1.5	50.1 ± 2.1	0.70
Birth head circumference (cm)	33.8 ± 1.3	33.9 ± 1.4	0.68
Birth body weight (g)	3012.7 ± 375.3	3118.7 ± 391.4	0.25
Low birth weight <2500g	2 (8.7)	4 (5.2)	0.62
Small for gestational age (SGA)	2 (8.7)	8 (10.4)	1.00
Body weight (kg)			
1-year-old	9.0 ± 1.0 (n=23)	9.2 ± 1.1 (n=66)	0.47
2-year-old	11.8 ± 1.3 (n=22)	12.2 ± 1.4 (n=60)	0.29
3-year-old	13.8 ± 1.6 (n=20)	14.5 ± 2.1 (n=45)	0.18
Body height (cm)			
1-year-old	75.4 ± 2.4 (n=23)	74.7 ± 2.6 (n=66)	0.24
2-year-old	86.4 ± 2.8 (n=22)	87.1 ± 3.6 (n=60)	0.45
3-year-old	94.0 ± 3.7 (n=20)	95.6 ± 4.7 (n=45)	0.19
Domains of the CDIIT test	(n=14)	(n=18)	
Attention	109.3 ± 16.9	108.2 ± 18.9	0.87
Perception	106.9 ± 13.6	106.4 ± 15.2	0.93
Memory	106.4 ± 22.9	107.6 ± 23.9	0.89
Reasoning	110.1 ± 15.3	110.8 ± 17.1	0.91
Concepts	105.3 ± 16.2	103.5 ± 20.9	0.79

Table 4. The risk factors for SGA using univariate analysis

Variable, Mean ± SD	SGA	Non-SGA	*p* value
Placental weight (g)	445.0 ± 47.9 (n=10)	514.9 ± 47.4 (n=90)	< 0.01
IGF-1 (ng/mL)	24.7 ± 10.5 (n=7)	40.1 ± 18.8 (n=69)	0.04
IGFBP-3 (ng/mL)	834.5 ± 363.7 (n=7)	759.1 ± 323.8 n(n=69)	0.56
Insulin (pmol/L)	22.7 ± 17.9 (n=7)	29.9 ± 29.3 (n=69)	0.53
Ghrelin (pg/mL)	1045.1 ± 241.6 (n=7)	774.3 ± 195.8 (n=69)	< 0.01

SGA, small for gestational age.

Figures

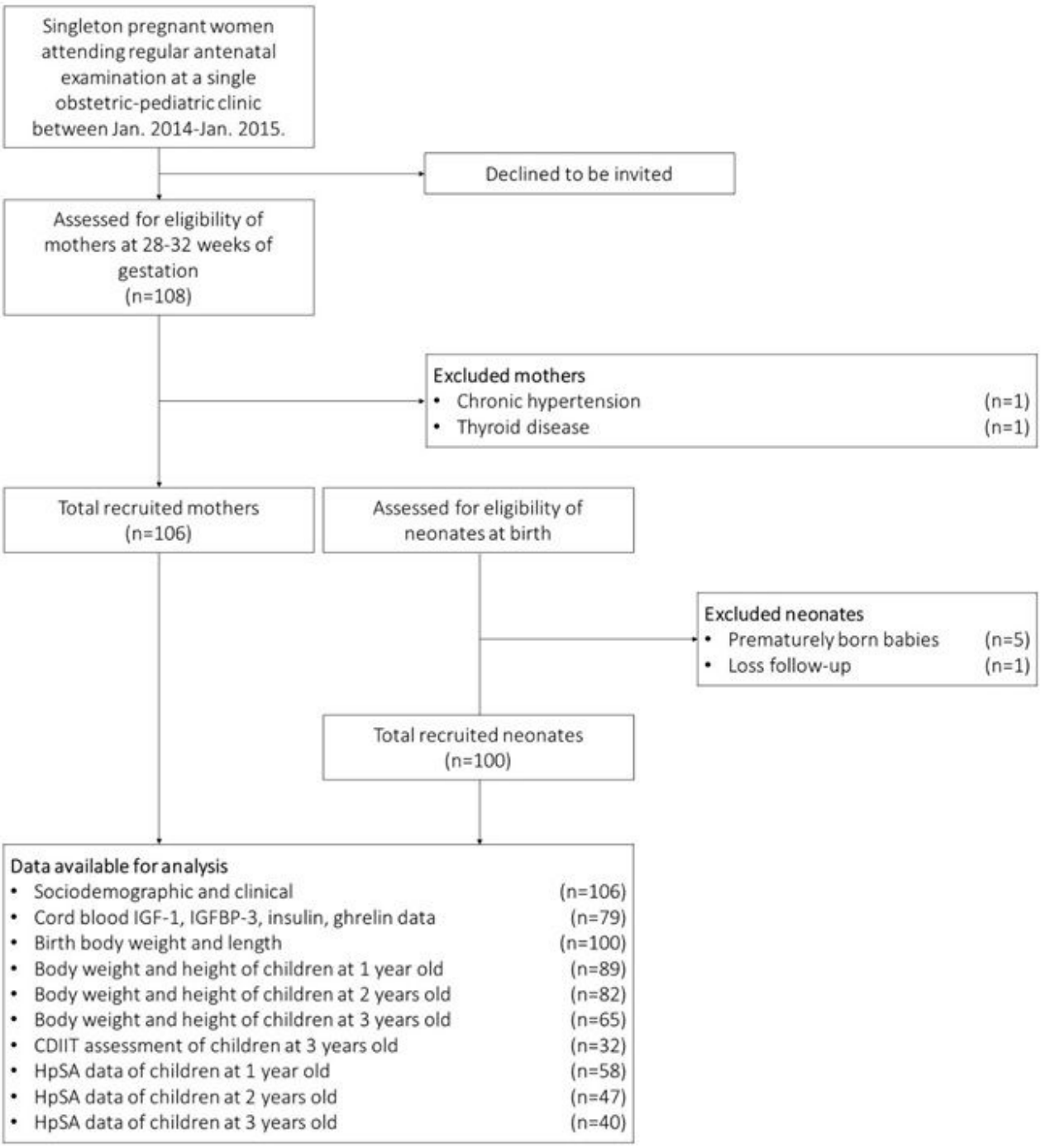

Figure 1

The workflow and case numbers of the study