Pregnancy-Induced Hypertension in Women Who Were Born Small

Svein Rasmussen, Lorentz M. Irgens

Abstract—We assessed whether a pregnant woman who was born small for gestational age has increased risk of pregnancy-induced hypertension (PIH), and whether the same applies to a pregnant partner of a man who was born small for gestational age. We linked generational data from the medical birth registry of Norway (1967–2005). Female and male newborns were identified as parents with 197 716 and 131 959 first or second pregnancies from 1998 to 2005, respectively. In the first pregnancy in women who were born with birth weight <2.5, 2.5 to 4.9, and 5 to 9.9 birth weight percentiles, odds ratios of PIH in general adjusted for smoking and maternal age were 1.5, 1.4, and 1.1, respectively, compared with percentile 25 to 75. In the second pregnancy, corresponding odds ratios were 1.5, 1.3, and 1.2, respectively. A similar trend was found in all of the subgroups of PIH. Women who were born below the 5th birth weight percentile were 2 to 3 times more likely to have preeclampsia with onset before 34 weeks of gestation than those with birth weight between the 25th and 75th percentiles (adjusted odds ratios: 1.8 to 2.8). Father’s birth weight for gestational age was not associated with mother’s development of PIH. In conclusion, women who were born growth restricted after normotensive pregnancies were more likely to develop PIH later in life. The lack of association with the father’s size at birth agrees with the hypothesis of fetal environmental origin of PIH, although maternal genetic transmission of susceptibility for PIH cannot be ruled out. (Hypertension. 2007;49:806-812.)

Key Words: hypertension ■ pregnancy ■ preeclampsia ■ birth weight ■ small for gestational age

Fetal growth restriction and pregnancy-induced hypertension (PIH; preeclampsia or transient hypertension) complicate a significant proportion of all pregnancies and predict later cardiovascular disease.1,2 Earlier studies have reported intergenerational recurrence of low birth weight,3 as well as preeclampsia.4 We have reported increased risk of preeclampsia and abruptio placentae in women with fetal smallness for gestational age in earlier pregnancies.5,6 On this basis, we proposed a hypothesis of a shared etiologic factor or recurrent pathophysiologic mechanism for fetal growth restriction, PIH, and abruptio placentae, all involving placental dysfunction.5,6 Clinical studies have reported that fetal growth restriction often precedes preeclampsia in the same pregnancy.7 Also, morphological studies suggest that PIH and fetal growth restriction in general might share a pathophysiologic mechanism. Placental dysfunction characterized by occlusive lesions in the maternal uteroplacental (spiral) arteries, caused by failure of fetal cells (trophoblasts) to invade the arteries in early pregnancy, has been observed in PIH and fetal growth restriction.8,9 This suggests that at least some cases of PIH differ from fetal growth restriction only in the maternal response to a shared placental pathology.10,11

If a genetic or environmental cause of placental dysfunction tends to recur from mother to daughter, and placental dysfunction is a necessary factor in PIH, it would be expected that a woman who herself was born small for gestational age (SGA) has an increased risk of PIH. In that case, a man who was born SGA might transmit increased risk of PIH to his partner in her pregnancy. Alternatively, an association of fetal smallness with later PIH would be consistent with the hypothesis of fetal origin of adult disease, which proposes that adult disease, such as chronic hypertension, originates in response to the prenatal environment or fetal undernutrition, independent of genetic background.12 A case–control study from New York state showed an inverse association of maternal birth weight with risk of PIH.13 However, we are not aware of studies that have explored the effect of SGA in both parents on later PIH. The objective of the present study was to assess whether a pregnant woman who was born SGA has an increased risk of PIH and whether the same applies to a pregnant partner of a man who was born SGA.

Methods

Population-Based Generational Data

Since 1967, all births in Norway are notified to the Medical Birth Registry of Norway based on compulsory notification.14 More than 97% of pregnant women receive standardized antenatal care.15 The registry is composed of medical data on all of the live births and...
abortions at ≥16 weeks' gestation, including abortions induced on medical indications. Data are transferred by the midwives to the notification form from the pregnancy record, which the women bring to the delivery unit. Within the ninth day postpartum, the notification form is completed and sent to the Medical Birth Registry. In December 1998, a revised version of the notification form was implemented to include new variables, like data on maternal smoking habits and subgroups of PIH, which are notified by the checking of boxes.\textsuperscript{14}

From 1967 to June 2005, 2 236 250 births were registered. Using the national identification number, female newborns were subsequently identified as mothers with 486 197 singleton births. Births from December 1998, when the revised notification form had been introduced, were included in the present study, totaling 257 994 mothers with births. Mothers born after pregnancies with chronic hypertension and multiple pregnancies were excluded. The study was confined to subsequent first and second pregnancies, which included 212 482 mothers with births. Mothers whose own birth weight (n = 378) or gestational age (n = 8954) was lacking were excluded, leaving 203 471 mothers with births for study. The main analyses were confined to 197 716 mothers and offspring after exclusion of 5755 mothers who were born after pregnancies with PIH.

We also examined whether father’s own birth weight influenced the risk of PIH in his partner. Among the 197 716 mothers with births, data on the father’s own birth (only singleton birth included), including birth weight and gestational age, were available in 131 859 cases (67%). Fathers whose own birth weight (n = 267) or gestational age (n = 7725) was lacking were excluded. The number of fathers with data on their own births was lower than for women, because they were generally older than the women (mean difference: 2 years) and, thus, fewer of their births were recorded in the Medical Birth Registry from 1967; 34% of mothers were born during 1967–1971, whereas 46% of fathers were born during the same period. For 1967–1976, the proportions were 74% and 86%, respectively. Additionally, 4% of the fathers were unknown and could not be identified.

**Definition and Subgroups of PIH**

Clinical criteria of PIH in Norway have been in accordance with the recommendations by the American College of Obstetricians and Gynecologists in 1972,\textsuperscript{16} which are also referred to in the Medical Birth Registry’s instructions for completion of the notification form. Transient hypertension implies PIH without proteinuria and with BP ≥140/90 mm Hg (1 or both values exceeded) or rise in systolic BP ≥30 mm Hg or diastolic BP ≥15 mm Hg after 20 weeks of gestation. Mild preeclampsia implies systolic BP 140 to 159 mm Hg, diastolic BP 90 to 109 mm Hg, rise in systolic BP ≥30 mm Hg, or diastolic BP ≥15 mm Hg and proteinuria ≥1+. Proteinuria is defined as excretion of ≥0.3 g per day, usually equivalent to ≥1+ on a urine reagent strip. Severe preeclampsia implies BP ≥160/110 mm Hg and/or proteinuria ≥2+.

**Statistical Analysis**

To achieve normal distribution of birth weight, we used Box-Cox power transformation. Birth weight was regressed against gestational age using fractional polynomials.\textsuperscript{17} To calculate gender and birth order–specific birth weight percentiles, birth order (1 or 2+) and fetal gender were added to the polynomial equation. The method of scaled absolute residuals was used to model SD against gestational age.\textsuperscript{18} The SD score (z score) for each observation was the distance in SDs from the mean regression line. The 2.5th, 5th, 10th, 25th, 75th, 90th, 95th, and 97.5th birth weight percentiles were calculated as SD score −1.96, −1.645, −1.282, −0.674, 0.674, 1.282, 1.645, and 1.96, respectively, which are widely used cutoff points in obstetrics. The associations of PIH in the subsequent pregnancy with SGA (below the 2.5th, 5th, or 10th birth weight percentile) in the parents own births were estimated by odds ratios (ORs) obtained from logistic regression analysis in which we adjusted for maternal age in years (≥19, 20 to 24, 25 to 29, 30 to 34, and ≥35), marital status, and maternal daily smoking at the beginning of pregnancy. We assessed the effect on the association of birth weight with PIH of chronic renal disease, chronic heart disease, rheumatoid arthritis, diabetes mellitus types 1 and 2, and gestational diabetes. We used SPSS for analysis. We confirm that research ethics committees in Norway regularly exempt research on anonymized registry data from ethical review.

**Results**

Women who were born SGA were more likely to develop PIH (Table 1). In the first pregnancy in women who were born with birth weight <2.5, 2.5 to 4.9, and 5 to 9.9 percentiles, ORs of PIH in general adjusted for smoking and maternal age were 1.5, 1.4, and 1.1, respectively, compared with 25th to 75th percentiles. In the second pregnancy, corresponding ORs were 1.5, 1.3, and 1.2, respectively. Thus, although the proportions of PIH were highest in first pregnancies (Table 1), the association of birth weight with later PIH was not dependent on birth order. A similar trend was found in all of the subgroups of PIH but was particularly evident in preeclampsia with onset before 34 weeks of gestation. Women who were born SGA below the 5th birth weight percentile were 2 to 3 times more likely to have early onset preeclampsia (before 34 weeks of gestation) than those with birth weight between 25th and 75th percentiles (adjusted ORs: 1.8 to 2.8). For all of the PIH subgroups, the occurrence of PIH in women who were large for gestational age (above the 90th birth weight percentile) and the reference group between the 25th and 75th percentiles was statistically non-different. In supplementary regression analyses, the effects of chronic renal disease, chronic heart disease, rheumatoid arthritis, diabetes mellitus types 1 and 2, and gestational diabetes on the association of SGA with PIH were negligible and not included in the final models. Limiting the analyses to mothers who were born at term (≥37 weeks of gestation) did not significantly change the effects; the effects of SGA on later PIH in mothers who were born preterm and at term were similar (data not shown). However, the numbers of women born both preterm and SGA were small, and the effect on PIH was nonsignificant. We also did supplementary analyses, including the 5755 mothers who were born after pregnancies with PIH, which did not reveal significantly changed effects (data not shown). Father’s birth weight for gestational age was neither associated with mother’s development of PIH in general (Table 2) nor subgroups of PIH (data not shown).

**Discussion**

Women who were born SGA more often had PIH, whereas men’s SGA was not associated with their pregnant partners’ risk of PIH.

**Strengths and Weaknesses: Possible Sources of Confounding**

A strength of this study is its large size. Based on the total Norwegian birth population, the study was most likely not affected by selection bias. Furthermore, data on SGA were collected prospectively, thereby precluding recall bias.

Some of the effect of SGA on later PIH might be explained by shared risk factors for fetal growth restriction and PIH, such as hereditary thrombophilia and maternal short stature, which have been associated with both conditions,\textsuperscript{19–21} but not...
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However, because these risk factors are uncommon or weakly associated with either SGA or PIH, they would not cause the associations. The association between SGA and later PIH is most likely not caused by low socioeconomical level, which has been reported to be only weakly associated or unassociated with PIH. Because of a lack of data, we were not able to include in the study excessive weight gain and prepregnancy weight, which, however, are both strong and common risk factors for preeclampsia and tend to increase fetal weight. Thus, adjust-

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consistently. However, because these risk factors are uncommon or weakly associated with either SGA or PIH, they would not cause the associations. The association between SGA and later PIH is most likely not caused by low socioeconomical level, which has been reported to be only weakly associated or unassociated with PIH. Because of a lack of data, we were not able to include in the study excessive weight gain and prepregnancy weight, which, however, are both strong and common risk factors for preeclampsia and tend to increase fetal weight. Thus, adjust-
ing for weight gain and prepregnancy weight would increase rather than decrease the effect of SGA on PIH. Moreover, birth weight may influence adult size (weight, height, or body mass index), and, therefore, maternal size would be considered as an intermediate factor in the causation of PIH. Such adjustment would, thus, not be justified. Additionally, although obesity becomes more prevalent in Norway, the Norwegian pregnancy population is still relatively lean, and recent evidence suggests that the association with obesity may be limited to late-onset PIH. Our database holds information on maternal smoking, which is a strong and common risk factor for fetal growth restriction and seems to be negatively associated with PIH. As expected, adjustment for smoking increased the association of SGA with later PIH (data not shown). The Medical Birth Registry also holds data on conditions like chronic renal disease, chronic heart disease, rheumatoid arthritis, diabetes mellitus type 1 and 2, and gestational diabetes. These conditions may also be regarded as intermediate in the effect of SGA on later PIH. Additionally, in supplementary analysis, the effects of these variables on the association of SGA with PIH were negligible, and they were not included in the final models.

Although preterm and term SGA may involve 2 different environmental effects on the fetus, limiting the analyses to mothers who were born at term did not significantly change the effects. The effects of SGA on later PIH in mothers who were born preterm and at term were similar. This indicates that preterm and term SGA both involve fetal malnutrition and have similar effects on later PIH.

Comparisons With Other Studies
We are not aware of studies that have explored the effect of SGA in both parents on later PIH. Our results agree with an American case–control study that also showed an association of maternal low birth weight with PIH. In this population-based study, which included mothers aged ≤28 years, 60% of the population was successfully linked, whereas linkage in the Norwegian Medical Birth Registry is considered almost complete. Three other studies also agreed with the results of the present study. However, these studies were too small (<350 cases) to allow subdivision of mother’s size at birth.

Genetic Influence or Fetal Origin of Adult Disease?
Our results that a woman’s SGA is associated with later PIH are consistent with the hypothesis of fetal origin of adult disease, which proposes that adult disease, such as chronic hypertension, occurs in response to the prenatal environment, or fetal undernutrition, independent of genetic background. However, our results would also lend support to a hypothesis that a shared genetic or environmental factor for fetal growth restriction and PIH tends to recur from mother to daughter. The fetal origin hypothesis proposes that undernutrition during fetal life or infancy increases the risk to develop coronary heart disease, type 2 and gestational diabetes, stroke, and hypertension later in life. In affluent countries, fetal starvation usually is a consequence of placental dysfunction likely caused by shallow invasion of fetal trophoblasts in the maternal spiral arteries. There is evidence to link low birth weight with endothelial dysfunction in infants and adults. Although longitudinal studies are needed to pursue endothelial function over time, previous studies indicate that endothelial dysfunction may be an inborn characteristic in subjects with fetal growth restriction that persists throughout childhood into adult life. The association of low birth weight with PIH is not limited to late-onset PIH; it is observed in both mothers and fathers. Additionally, the association of SGA with PIH is not limited to term birth; it is also observed in preterm birth.
weight with endothelial dysfunction in adults, which is considered necessary in the development of PIH,\textsuperscript{10} may explain the increased risk of PIH and cardiovascular disease later in life.\textsuperscript{30,31} Alternatively, congenital nephron deficit may increase the risk of later PIH. It has been proposed that undernourished fetuses have fewer cells in key organs, such as the kidneys, and that hypertension is initiated by the reduced number of glomeruli found in persons who were growth restricted at birth.\textsuperscript{33,34} As a consequence, the filtration surface area decreases, which limits the renal sodium excretion and eventually leads to essential hypertension. This theory has been supported by morphological studies reporting that those being treated for hypertension had fewer glomeruli.\textsuperscript{35} Possibly, the risk of PIH can be increased by a similar mechanism.

However, the association of SGA and later PIH is also consistent with the hypothesis of a shared genetic factor for fetal growth restriction and PIH. This agrees with evidence of intergenerational recurrence and increased risk of recurrence between births in the same mother of placental dysfunction-related disorders, like PIH, fetal growth restriction, and abrupto placenta.\textsuperscript{3–5,36,37} Thus, women with fetal smallness in earlier pregnancies have increased risk of preeclampsia and abrupto placenta.\textsuperscript{5,6} Consistent with a shared genetic background for fetal growth restriction and PIH, morphological studies have reported that occlusive changes in the spiral arteries, likely caused by inadequate fetal trophoblast invasion early in pregnancy, have been found in preeclampsia, as well as normotensive fetal growth restriction, indicating a fetal component in the mechanism.\textsuperscript{8,9} It has been proposed that these fetus-induced decidual (placental bed) changes tend to recur from 1 pregnancy to another in the same woman.\textsuperscript{38} Some cases of fetal growth restriction might differ from preeclampsia only in the maternal response to a shared placental pathology.\textsuperscript{10,11} It has been postulated that substances, such as soluble fms-like tyrosine kinase and lipid peroxides, produced or induced by the poorly perfused placenta\textsuperscript{39} enter the maternal circulation and cause endothelial dysfunction, which is clinically manifested as the systemic maternal syndrome of preeclampsia.\textsuperscript{10} Consistently, Levine et al\textsuperscript{40} reported increased levels of soluble fms-like tyrosine kinase in women who later developed preeclampsia. Subsequently, soluble fms-like tyrosine kinase binds to vascular endothelial growth factor and placental growth factor, inhibiting their interaction with endothelial receptors on the cell surface and thereby inducing endothelial dysfunction.\textsuperscript{40}

Among numerous genes that have been reported for susceptibility to both fetal growth restriction and preeclampsia, the set of genes that express thrombophilia is a candidate.\textsuperscript{23,41} Other sets of genes are considered more specific for endothelial dysfunction, such as the endothelin-1 gene,\textsuperscript{42} and would, thus, be candidate genes for expression of the maternal response to placental dysfunction.

**Paternal Genes**

The lack of association between men’s birth size and PIH in their pregnant partners is consistent with the hypothesis of fetal origin of adult disease, which links fetal starvation, independent of genetic background, to adult disease. The lacking paternal effect was unexpected, because it has been shown that men who had fathered a preeclamptic pregnancy in 1 woman had an increased risk of fathering a preeclamptic pregnancy in another woman.\textsuperscript{37} However, although significant, this increased paternal recurrence risk of preeclampsia was small. One might expect an even lower effect of men’s birth size on later preeclampsia. The lacking paternal effect in the present study is consistent with 2 alternative mechanisms. In a pregnancy to a woman who was born growth restricted, maternal susceptibility genes for PIH may operate in addition to susceptibility genes for PIH from either fetus’s parent, which operate through the fetus or the placenta. However, a father’s susceptibility gene for PIH would only be passed through the fetus or the placenta and will not be expressed as PIH. Alternatively, susceptibility to PIH is caused by intragenetic programming,\textsuperscript{12} which cannot be transmitted to a partner. The lacking paternal effect is also consistent with the earlier reported lower paternal versus maternal intergenerational recurrence rates of preeclampsia,\textsuperscript{4} low birth weight,\textsuperscript{3} and the increased subsequent cardiovascular mortality in mothers with preeclampsia and not in their partners.\textsuperscript{2}

**Perspectives**

The finding of our study provide evidence that women who were born growth restricted after normotensive pregnancies were more likely to develop PIH later in life, whereas poor fetal growth in men was not associated with PIH in their pregnant partners. The lack of association with the father’s size at birth agrees with the hypothesis of the fetal environmental origin of PIH, although maternal genetic transmission of susceptibility for PIH cannot be ruled out. Alternatively, an interaction of fetal environment with maternal genetic susceptibility causes the association of poor fetal growth to later PIH. Future genetic or large-scale family studies are needed to confirm our results and to rule out paternal genetic influence on the effect on fetal growth restriction on PIH, such as studies on whether men who had fathered a pregnancy with fetal growth restriction are more likely of fathering a pregnancy with PIH in another woman.

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**Disclosures**

None.

**References**


Pregnancy-Induced Hypertension in Women Who Were Born Small
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