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Preeclampsia mediates the association between shorter height and increased risk of preterm delivery

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Abstract

Background: Maternal short stature has been observed to increase the risk of preterm birth; however, the aetiology behind this phenomenon is unknown. We investigated whether preeclampsia, an obstetric complication that often leads to preterm delivery and is reported to have an inverse association with women's height, mediates this association.

Methods: We studied 218 412 women with no underlying diseases before pregnancy, who delivered singletons from 2005 to 2011 and were included in the Japan Society of Obstetrics and Gynecology perinatal database, which is a national multi-centre-based delivery database among tertiary hospitals. We assessed the risk of preterm delivery in relation to height using multivariate analysis, and how the association was mediated by risk of preeclampsia using mediation analysis.

Results: Each 5-cm decrement in height was associated with significantly higher risk of preterm delivery [relative risk 1.20; 95% confidence interval (CI): 1.13, 1.27] and shorter gestational age (−0.30; 95% CI: -0.44, -0.16 weeks). Mediation analysis showed that the effect of shorter height on increased risk of preterm delivery, due to an indirect effect mediated through increased risk of preeclampsia, was substantial for shorter gestational age (48%), as well as risk of preterm delivery (28%). When examining the three subtypes of preterm delivery separately, mediated effect was largest for provider-initiated preterm delivery without premature rupture of membranes (PROM) (34%), compared with spontaneous preterm delivery without PROM (17%) or preterm delivery with PROM (0%).

Conclusions: Preeclampsia partially mediates the association between maternal short stature and preterm delivery.

Key words: Height, preeclampsia, preterm delivery

Key Messages

- Maternal height has been shown to be inversely associated with increased risk of preterm delivery over many populations.
- Preeclampsia is a major cause of preterm delivery, and is reported to be of increased risk among shorter women.
- In this study, we found that preeclampsia partially mediated the association between shorter height and increased risk of preterm delivery.

Introduction

Preterm birth, or birth before 37 completed weeks of gestation, is the leading cause of neonatal mortality, contributing to over one-third of the world's estimated 3 000 000 neonatal deaths per year.[1,2,3] Even after surviving the neonatal period, infants born preterm are at increased risk for delayed childhood development and low economic productivity.[4] Acknowledgment of the large public health impact of preterm birth has led to many initiatives aiming to prevent preterm birth by providing comprehensive antenatal care, childbirth services and emergency obstetric care.[5–7]

Among many identified risk factors of preterm birth, maternal short stature has been widely observed to increase the risk of preterm birth.[8,9] The aetiology behind this association remains unexplained, with the most commonly used suggestion being that short stature may limit the uterine volume for fetal growth.[8,10] However, results from observational studies do not fully support the hypothesis of a tendency for a large infant being delivered early from a shorter mother where the uterus may be disproportionate in size to the infant. For example, paternal height (which is strongly correlated with fetal growth) lacks association with gestational age,[11,12] and maternal short stature is inversely associated with preterm delivery even at the lower gestations when the fetus is still small.[13]

On the other hand, recent studies show that maternal short stature increases the risk of preeclampsia[14–17] as well as placental abruption,[16] two strong indicators of placental ischaemia, a condition known to be the leading cause of medically indicated preterm deliveries.[18–20] Further, several reports showed that short stature also increases the risk of stillbirth,[21,22] whereas earlier delivery when fetal distress is detected is needed to prevent stillbirths. Thus, it is possible that the frequently observed association between shorter height and shorter gestational age may not only be due to physiological 'early filling', but due to increase in earlier deliveries due to higher risk of pregnancy complications among shorter women. However, previous studies[8,9] have not considered the possible role that pregnancy complications may play in the relationship connecting short stature and preterm delivery.

The objective of this study was to examine the extent to which preeclampsia mediates the association between short stature and preterm delivery. To address this objective, we analysed data from the Japan Society of Obstetrics and Gynecology (JSOG) perinatal database, a large national institutional-based obstetrics database in Japan.

Methods

The study population and data collection methods have been previously described in detail.[16,23–25] Briefly, the JSOG perinatal database is an ongoing registry based on a national collaboration of obstetric departments from 149 tertiary hospitals in Japan, collecting individual patient data on all live births and stillbirths delivered at 22 weeks or after, from medical charts using a standardized format. The JSOG Perinatal Committee annually reviews the submitted data for data quality and contacts institutes for correction if a substantial portion contains erroneous or missing data. The data for 2004–11 were recently linked to vital statistics data that verified their accuracy and showed that this registry covers 6.5% of all national births.[23]

There were 280 204 registered women with no medical conditions (respiratory, gastrointestinal, hepatic, renal, haematological, cardiovascular, metabolic, mental disease or hypertension) before pregnancy, who delivered

singletons with no congenital anomaly between April 2005 and December 2011, at 22 weeks of gestation or laer. We excluded 4502 with missing data on either parity, age at delivery, gestational weight gain, infant sex, gestational age or birthweight, or inconsistent combination of birthweight and gestational age (using the method proposed by Alexander *et al.*[26]). Main analysis was based on 218 412 women, further excluding subjects with missing or unreliable [> 4 standard deviations (SD) or < -4 SD of the population] data on height ($n = 44\,780$) and missing or unreliable (> 20 kg considered unreliable) data on pre-pregnancy weight ($n = 12\,510$).

The primary exposure of interest was self-reported maternal height. As only 5% of the database had reported height in millimetres, all measurements were rounded to the nearest centimetre. The primary outcome of interest was preterm birth, defined as less than 37 completed weeks of gestation, based on best obstetric estimates of gestational age estimated from the last menstrual period and corrected by ultrasound measurements during the first trimester. Similarly, we defined early preterm birth as delivery at less than 34 completed weeks of gestation, and late preterm birth as delivery at 34 to 36 completed weeks of gestation. From data of gestational age at delivery, onset of labour and mode of delivery, as well as existence of premature rupture of membranes (PROM), we created three subtypes of preterm delivery[2,27]: (i) preterm delivery with PROM; (ii) provider-initiated preterm delivery with no PROM (defined as preterm delivery by pre-labuor cesarean delivery or labour induction with no PROM); and (iii) spontaneous preterm delivery with no PROM (defined as preterm delivery with spontaneous onset of labour and no PROM). For these classifications, both live births and stillbirths were included; however, as stillbirth is the unfortunate outcome of not being able to deliver when the fetus is under distress, we also observed stillbirth as a secondary outcome.

Our mediator of interest was preeclampsia. Preeclampsia was diagnosed clinically by obstetricians in each hospital using a unified national guideline in line with the International Society for the Study of Hypertension in Pregnancy,[28] defined as systolic blood pressure over 140 mmHg or diastolic blood pressure above 90 mmHg that emerges after 20 weeks' gestation with significant proteinuria $\geq$ 300 mg/day.

Statistical Analysis

First, baseline characteristics were compared by trend analysis using quartiles of height: Quartile 1 (132–155 cm; $n = 54\,603$); Quartile 2 (155–158 cm; $n = 54\,603$); Quartile 3 (158–162 cm; $n = 54\,603$); Quartile 4 (162–183 cm; $n = 54\,603$). In the construction of the quartiles, women with same height at the quartile cutpoints were randomly assigned to the lower or higher quartile, to prevent uneven number of subjects in the categories. Next, we used multivariable Poisson regression to estimate risk ratios (RR) and 95% confidence intervals (CI) for preterm delivery, as well as three preterm delivery subtypes (provider-initiated with no PROM, spontaneous with no PROM, and PROM) and stillbirth, for each quartile of maternal height. Linear regression was used to estimate the effect of maternal height on gestational age.

After confirming the linearity of the association between height and the outcomes through these analyses, we conducted mediation analysis to evaluate the separate direct and indirect (mediated by preeclampsia) effects of each 5-cm increase in height on gestational age and risk of preterm delivery and stillbirth.

All analyses were adjusted by maternal age, parity, smoking status, pre-pregnancy body mass index (BMI) (calculated from self-reported height and self-reported pre-pregnancy weight),[29] and infant sex, which are known risk factors according to previous literature.[30,31] Adjustments were also made for maternal year of birth—to account for an increase in maternal height over the years in Japan[32]—as well as abnormal glucose tolerance (either pre-existing diabetes or gestational diabetes mellitus based on recommendations from the International Association of Diabetes in Pregnancy Study Groups[33]), which has recently been reported to be inversely associated with height.[34] Whereas the main analyses were conducted among women with complete data, we also performed sensitivity analyses that included the 44 780 women with missing height and 12 210 with missing pre-pregnancy weight data after multiple imputation (with 30 imputations) to fill in these values.

Mediation analysis hypothesizes that the total effect of maternal height (X) on an adverse outcome (Y) consists of a direct effect and an indirect effect [i.e. mediated by preeclampsia (M)], and calculates the proportion of the total effect that is indirect (i.e. mediated). Such an analysis enabled us to estimate to what extent the increased risk of preeclampsia among shorter mothers was responsible for increased risks in other outcomes. The original theoretical model proposed by Baron and Kenny[35] had crudely calculated this proportion as 1- c'/c from the following three models: (i) one model estimating the total effect (c) of X on Y; (ii) one model estimating the direct effect (c') of X on Y with M included as a covariate; and (iii) one model estimating the effect of X on M. However, it has been shown that the lack of account of possible exposure-mediator interactions could miscalculate the mediation effect; thus, we used an improved model proposed by VanderWeele

et al.[36,37] As this method cannot accommodate the uncertainty in measures produced by multiple imputation, this analysis was conducted on mothers with complete data.

All descriptive and statistical analyses were performed using STATA version 13 (STATA Corp, College Station, TX), with mediation analysis conducted using the command 'paramed' available in the program. The protocol for this study was approved by the Institutional Review Board of the National Center for Child Health and Development on January 28, 2016 (No. 1102).

Results

Our analysis found that among 218 412 women, 28 323 (13.0%) had preterm delivery, among which 6013 (21%) were provider-initiated preterm deliveries with no PROM, 14 754 (52%) were spontaneous preterm deliveries with no PROM and 7556 (27%) were preterm delivery with PROM; 1317 (0.6%) women delivered a stillbirth, and 5434 (2.5%) women experienced preeclampsia. Women in higher quartiles of height were thinner, older, more likely to be primiparous and smoked less. They also had significantly lower prevalence of all subtypes of preterm delivery, as well as stillbirth delivery, preeclampsia and abnormal glucose tolerance (Table 1). Average gestational ages for the four categories were 38.0 (standard deviation: 2.7) weeks, 38.1 (2.7) weeks, 38.2 (2.6) weeks and 38.3 (2.5) weeks, from shortest to tallest, respectively.

In the adjusted model, we found that quartiles of increasing height was significantly associated with gestational age, and inversely associated with preterm delivery, stillbirth and preeclampsia (Table 2). Women in the lowest

Table 1. Maternal and infant characteristics by quartiles of maternal height among 218 412 women

Maternal and infant characteristics	Quartiles (Q) of height								
	Q1 (n = 54603) 132–155 cm (mean 151.4)		Q2 (*n* = 54603) 155–158 cm (mean 156.4)		Q3 (*n* = 54603) 158–162 cm (mean 159.9)		Q4 (*n* = 54603) 162–183 cm (mean 165.1)		*P*-value
	No.	%	No.	%	No.	%	No.	%	
Maternal age									
< 20 years	1071	2.0	748	1.4	636	1.2	494	0.9	< 0.001
20–35 years	39365	72	38828	71	38302	70	38217	70	
> 35 years	14167	26	15027	28	15665	29	15892	29	
Prepregnancy BMI									
< 18.5 kg/m^2	9143	17	9966	18	10106	19	11620	21	< 0.001
18.5 to 25 kg/m^2	39002	72	39009	71	39060	72	37965	70	
> 25 kg/m^2	6458	12	5628	10	5437	10	5018	9.2	
Parity									
0	26792	49	27296	50	27662	51	28528	52	< 0.001
1< =	27811	51	27307	50	26941	49	26075	48	
Smoking									
Yes	2687	4.9	2592	4.7	2387	4.4	2289	4.2	< 0.001
No	42436	78	42479	78	42552	78	42895	79	
Missing	9480	17	9532	18	9664	18	9419	17	
Infant sex									
male	28167	52	28212	52	27962	51	28103	52	0.456
Female	26436	48	26391	48	26641	49	26500	49	
Pregnancy complications	No.	%	No.	%	No.	%	No.	%	
Preeclampsia	1626	3.0	1372	2.5	1251	2.3	1185	2.2	< 0.001
Preterm delivery	8116	15	7240	13	6752	12	6215	11	< 0.001
- Provider-initiated with no PROM	3323	6.1	3009	5.5	2745	5.0	2453	4.5	
- spontaneous, with no PROM	4793	9.4	4231	8.2	4007	7.7	3762	7.2	
- with PROM	1692	3.1	1540	2.8	1428	2.6	1353	2.5	
Early preterm delivery	4322	7.9	3746	6.9	3532	6.5	3154	5.8	< 0.001
Late preterm delivery[a]	2102	3.8	1954	3.6	1792	3.3	1708	3.1	< 0.001
Stillbirth	355	0.7	288	0.7	361	0.6	313	0.5	0.027
Abnormal glucose tolerance	1938	3.6	1328	3.0	1777	2.9	1565	2.7	< 0.001

P-value calculated for test of trend.

[a]Percentage calculated using births of gestational age 34 weeks or above.

Table 2. Association between maternal height and adverse pregnancy outcomes among 218412 women

	Gestational age [weeks (95% CI)]	Preterm delivery [RR (95% CI)]	Provider-initiated preterm delivery with no PROM [RR (95% CI)]	Spontaneous preterm delivery with no PROM [RR (95% CI)]	Preterm delivery with PROM [RR (95% CI)]
Q1	−0.34 (−0.37, -0.31)	1.29 (1.25, 1.34)	1.24 (1.16, 1.33)	1.31 (1.26, 1.36)	1.23 (1.16, 1.31)
Q2	−0.20 (−0.23, -0.17)	1.16 (1.12, 1.20)	1.14 (1.06, 1.23)	1.17 (1.12, 1.22)	1.15 (1.07, 1.23)
Q3	−0.10 (−0.13, -0.07)	1.09 (1.06, 1.13)	1.05 (0.98, 1.12)	1.11 (1.07, 1.15)	1.06 (1.00, 1.13)
Q4	Reference	Reference	Reference	Reference	Reference

	Early preterm delivery (< 34 weeks of gestation) [RR (95% CI)]	Late preterm delivery (34 to 36 weeks of gestation)[a] [RR (95% CI)]	Stillbirth [RR (95% CI)]
Q1	1.32 (1.26, 1.39)	1.29 (1.25, 1.35)	1.21 (1.04, 1.41)
Q2	1.21 (1.15, 1.28)	1.13 (1.09, 1.19)	1.21 (1.03, 1.41)
Q3	1.12 (1.07, 1.18)	1.08 (1.04, 1.13)	1.10 (0.94, 1.28)
Q4	Reference	Reference	Reference

Quartiles were as follows: Q1 (132–155cm), Q2 (155–158cm), Q3 (158–162cm), Q4 (162–183cm).
Adjusted for maternal year of birth, maternal age, parity, pre-pregnancy body mass index, smoking status, glucose tolerance status and infant sex.
[a]Sample size is 206, = 882 deliveries at 34 weeks or above.

Table 3. Direct effects and indirect (mediated by preeclampsia) effects of each 5-cm decrement in maternal height on gestational age, preterm delivery and stillbirth

	Total effect	Natural direct effect	Natural indirect effect	% mediated
All births ($n = 218412$)				
Gestational age [weeks (95% CI)]	−0.30 (−0.44, −0.16)	−0.16 (−0.19, −0.12)	−0.15 (−0.22, −0.07)	48.3%
Preterm delivery [RR (95% CI)]	1.20 (1.13, 1.27)	1.14 (1.08, 1.19)	1.06 (1.04, 1.07)	28.4%
Provider-initiated with no PROM [RR (95% CI)]	1.15 (1.04, 1.28)	1.10 (1.02, 1.18)	1.05 (1.02, 1.08)	33.5%
Spontaneous, with no PROM, [RR (95% CI)]	1.10 (1.05, 1.15)	1.08 (1.06, 1.10)	1.02 (0.98, 1.06)	16.5%
Spontaneous with PROM, [RR (95% CI)]	1.09 (0.78, 1.53)	1.10 (0.95, 1.27)	1.00 (0.82, 1.21)	0.0%
Early preterm delivery [RR (95% CI)]	1.25 (1.11, 1.40)	1.14 (1.03, 1.26)	1.10 (1.08, 1.11)	39.2%
Stillbirth [RR (95% CI)]	1.22 (0.87, 1.71)	1.16 (0.89, 1.51)	1.06 (1.00, 1.11)	25.6%
Limited to 34 weeks and over ($n = 206882$)				
Gestational age [weeks (95% CI)]	−0.14 (−0.25, −0.04)	−0.09 (−0.11, −0.08)	−0.05 (−0.09, 0.00)	33.5%
Late preterm delivery [RR (95% CI)]	1.20 (1.11, 1.30)	1.13 (1.07, 1.20)	1.06 (1.03, 1.08)	28.9%

Adjusted for maternal year of birth, maternal age, parity, pre-pregnancy body mass index, smoking status, glucose tolerance status and infant sex.

quartile of height had significantly shorter gestational age [-0.34 (95% CI: −0.37, −0.31) weeks], as well as higher risk of preterm delivery [RR 1.29 (95% CI: 1.25, 1.34)] and stillbirth [RR 1.21 (95% CI: 1.04, 1.41)] compared with women in the highest quartile. Results were similar in sensitivity analysis based on all subjects which used imputed values in place of missing or implausible height or weight measures as well as smoking status (see Appendix, available as Supplementary data at *IJE* online).

Next, as shown in Table 3, in the adjusted model accounting for possible mediation by preeclampsia as well as any possible exposure-mediator interactions, the total effect (direct and preeclampsia-mediated indirect effect) of each 5-cm decrement in height was associated with an increased risk of preterm delivery [RR 1.20 (95% CI: 1.13, 1.27) and stillbirth [RR 1.22 (95% CI: 0.87, 1.71)], and decreasing mean weeks in gestational age [-0.30 (95% CI: −0.44, −0.16)]. When evaluating the effect mediated indirectly through preeclampsia, each 5-cm decrement showed an increased risk of preterm delivery [RR 1.06 (95% CI: 1.04, 1.07)] and stillbirth [RR 1.06 (1.00, 1.11)], and decreasing mean weeks in gestational age [-0.15 (95% CI: −0.22, −0.07)]. Among subtypes of preterm delivery, the indirect effect mediated by preeclampsia was largest for risk of provider-initiated preterm delivery with no PROM [RR 1.05 (95% CI: 1.02, 1.08) per 5 cm], followed by risk of spontaneous preterm delivery with no PROM [RR 1.02 (95% CI: 0.98, 1.06) per 5 cm]; an effect on risk of preterm delivery with PROM was undetectable [RR 1.00 (95% CI: 0.82, 1.21) per 5 cm]. The estimated proportion of the effect of height due to an indirect effect mediated through increased risk of preeclampsia was substantial for shorter gestational age (48.3%), preterm delivery (28.4%) and stillbirth (25.6%). Among subtypes of

preterm delivery, mediation was largest for provider-initiated preterm delivery with no PROM (33.5%), followed by spontaneous preterm delivery with no PROM (16.5%) and null for preterm delivery with PROM (0.0%).

Discussion

In a large sample of healthy Japanese women who delivered singletons, we observed that increased risk of preeclampsia partially mediates the association between shorter maternal height and increased risk of preterm birth. The mediated effect was largest for provider-initiated preterm delivery with no PROM, but an effect was also observed for spontaneous preterm delivery with no PROM. No mediation effect was observed for preterm delivery with PROM. Our findings suggest that the robust association between height and preterm delivery, which has been observed among many populations,[8,9] can at least be explained in part by the increased risk of a major obstetric complication, preeclampsia,[14,17] in women of shorter height.

In our study we found a linear association between height and gestational age, as has been observed across diverse populations of numerous ethnicities and among high-, low- and middle-income countries.[8,9] The finding that risk of both early preterm and late preterm birth increases with shorter stature is consistent with recent reports from Sweden, which found similar effects of height on risk of both preterm and very preterm births.[13] Our study also replicates findings on the association between shorter height and increased risk of stillbirth that have been reported from Scotland[21] and Canada.[22]

To our knowledge, this study is the first to suggest that a pathological obstetric complication partially mediates the association between shorter maternal height and increased risk of preterm delivery. As recent studies show that shorter height is associated with increased risk of preeclampsia,[14–17] and preeclampsia plays a key role in preterm delivery,[18–20] such a hypothesis is biologically plausible. The common interpretation of increased risk of preterm delivery and shorter gestation among shorter women has been that a shorter woman would have a smaller uterus subject to 'early filling', but paternal height—which affects fetal growth (most likely genetically) equally as strongly as maternal height[10,38, 39]—has consistently shown no relationship with gestational age.[11,12] Also such 'early filling' would only occur later in pregnancy, and fails to explain why shorter women have increased risk of very preterm and extremely preterm births[13] when the fetus weighs merely approximately 500–1500 g. The hypothesis suggested by our results, that the association is not purely due to anatomical issues related to the woman's uterus or pelvis, but has a pathological component due to pregnancy complications, provides a plausible interpretation that does not conflict with these findings.

We found that the proportion of the effect of height, mediated through preeclampsia, was larger for provider-initiated preterm delivery (33.5%) and spontaneous preterm delivery with no PROM (16.5%), compared with preterm delivery with PROM (0%). Hypertensive disorders in pregnancy are a major determinant of provider-initiated preterm delivery, and intrauterine infections such as chorioamnionitis are considered to be the more common cause of PROM.[27] Thus our results, showing differing magnitudes of mediation that are consistent with the current understanding of hypothesized mechanisms across the preterm subgroups, provide additional confidence in the interpretation that pregnancy complications may partially be responsible for why shorter women have higher risk of preterm delivery.

We also observed the mediated effect of height on preterm delivery to be stronger for early (39.2%) compared with late (28.9%) preterm deliveries. As preeclampsia is a leading indication for delivery, these results suggest that the link between maternal height and preterm delivery is mediated more strongly by preeclampsia with onset at earlier gestations compared with those which occur later. Interestingly, long-term follow-up of women with preeclampsia also showed differences in risk of hypertension and cardiovascular disease (CVD) later in life[40–42] by timing of preeclampsia onset, i.e. risk of future CVD was highest among those whose onset of preeclampsia was early (before 34 weeks of gestation) compared with those with later onset (as well as those with no preeclampsia).[42] These similarities in association, indicating a role for preeclampsia timing, together with the observed inverse association between adult height and both cardiovascular diseases (CVD)[43] and preeclampsia[14–17] risk, suggest a potentially complicated interplay between adult height, the timing of preeclampsia, and ultimately a dual effect on the fetus through preterm delivery and the mother's long-term health risks.

Further investigation is necessary to determine whether this mediated effect is influenced by genetic or environmental factors. Whereas nearly 80% of height is determined genetically, it is thought that 20% is modifiable by early life factors.[44] Thus shorter height may reflect the accumulation of adverse early life exposures (such as fetal, dietary, social and psychological circumstances),[44,45] which are known to be related to hypertension later in life.[43,44,46] On the other hand, a recent Mendelian randomization study using data on genome-wide single nucleotide polymorphisms concluded that the effect of maternal height on gestational age was transmitted through a phenotypic causal mechanism influenced by maternal genetics.[10] Thus the mediation could be due to genetically-driven phenotypes associated with preeclampsia.[47]

Our study has certain limitations. First, height was not measured but self-reported, and hence may not be precise.[48] Non-differential measurement error, as well as overestimation which has been reported to occur particularly among shorter women,[49] may have led to an underestimation of the effect of height on outcomes. Second, our mediation analysis would be subject to unmeasured confounding, due to a confounder that has an effect on both the mediator and outcomes of interest. However, even if we assumed substantial unmeasured confounding (for instance, assuming the effect of unmeasured confounding (U) on gestational age to be four times, and the effect of U on preeclampsia to be three times), the mediating effect would still be substantially large (28.9%). Third, although average height (157.9 cm) and prevalence of pregnancy-induced hypertension (systolic blood pressure over 140 mmHg or diastolic blood pressure above 90 mmHg that emerges after 20 weeks' gestation) in our study (3.9%) were similar to national figures (157.8 cm and 3.5%, respectively), our study was based on a birth registry of tertiary hospitals (which accept referrals from smaller hospitals), and may have included more women with higher social and medical risks compared with the general population.[50,51] Thus, although our study was fairly large, future studies on whether our findings are replicable in other populations should be encouraged.

Our study adds a new piece to the puzzle that may explain the consistently observed association between height and preterm delivery.[8,9] In addition to anatomical restrictions of the smaller pelvis, an increased risk of pathological complications associated with shorter height may explain this association.

Supplementary Data

Supplementary data are available at *IJE* online.

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Author Contributions

N.M. initiated the concept, designed the study, performed the analysis and wrote the initial manuscript. K.O. gave critical comments on the interpretation of the results and revised the draft. K.Y.U. gave critical comments on the study design, analytical methods, assisted in the interpretation of the results and revised the draft. S.S. and S.S. collected the data and assisted in the interpretation of the results. H.S. assisted in the interpretation of the results and revised the draft. K.Y.U. and Emma Barber have carefully edited the English language.

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