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Title: Isolated gestational proteinuria preceding the diagnosis of preeclampsia – an observational study

Running headline: Proteinuria preceding preeclampsia

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Conflict of Interest

The authors have no conflicts of interest to declare.

Key message

Isolated gestational proteinuria (IGP), defined as protein:creatinine ratio > 0.27 mg/mg (30 mg/mmol) in the absence of hypertension, is a prominent risk factor for developing preeclampsia (relative risk, 13.1 compared to women without IGP).

Abstract

Introduction: Some pregnant women develop significant proteinuria in the absence of hypertension. However, clinical significance of isolated gestational proteinuria (IGP) is not well understood. This study aimed to determine the prevalence of IGP in singleton pregnancies and the proportion of women with IGP who subsequently developed preeclampsia (IGP-PE) among all PE cases.

Material and Methods: This was an observational study of 6819 women with singleton pregnancies at 12 centers, including 938 women with at least once determination of protein-to-creatinine ratio (P/Cr). Significant proteinuria in pregnancy (SPIP) was defined as P/Cr (mg/mg) level > 0.27. IGP was defined as SPIP in the absence of hypertension. Gestational hypertension (GH) preceding preeclampsia (GH-PE) was defined as preeclampsia (PE) in which GH preceded SPIP. Simultaneous PE (S-PE) was defined as PE in which both SPIP and hypertension occurred simultaneously.

Results: IGP and PE were diagnosed in 130 (1.9%) and 158 (2.3%) of 6819 women, respectively. Of 130 IGP women, 32 (25%) progressed to PE and accounted for 20% of all PE women. Thus, women with IGP had a relative risk of 13.1 (95% CI; 9.2 – 18.5) for developing PE compared to those without IGP (25% [32/130] vs. 1.9% [126/6689]). At diagnosis of SPIP, P/Cr levels already exceeded 1.0 more often in women with S-PE than in those with IGP-PE (67% [33/49] vs. 44% [14/32], respectively, $p = 0.031$).

Conclusions: IGP is a risk factor for PE, and IGP-PE accounts for a considerable proportion (20%) of all PE.

Key words: disease pregnancy, pregnancy outcome, proteinuria pregnancy, protein to creatinine ratio, preeclampsia

Abbreviations: GH, gestational hypertension; GH-PE, GH preceding preeclampsia; GW, gestational week; IGP, isolated gestational proteinuria; IGP-PE, IGP preceding PE, P/Cr, protein-to-creatinine ratio; PE, preeclampsia; S-PE, simultaneous PE; SPIP, significant proteinuria in pregnancy

Introduction

Preeclampsia (PE) is a life-threatening complication (1) and occurs in approximately 2.3% of Japanese women (2). Hospitalized care and regular blood tests are currently recommended for women diagnosed with PE (3, 4). A diagnosis of PE is made in women developing both hypertension and significant proteinuria in pregnancy (SPIP), although it has recently been proposed that preeclampsia can be diagnosed in hypertensive women with alterations in the liver function, kidney function, and hematology in the absence of SPIP (5 – 7). The time between diagnosis of PE and delivery is relatively short, within 2 weeks in most cases (8, 9). Early diagnosis of SPIP allows early diagnosis of PE and early initiation of intensive monitoring. Hospitalized care and regular blood tests would theoretically facilitate early detection of adverse conditions associated with PE, such as thrombocytopenia, liver and renal involvement, and posterior reversible encephalopathy syndrome, thus leading to earlier delivery with improved outcomes, although evidence is lacking.

Maternal organ systems that are susceptible to excessive inflammation and endothelial damage in PE are the central nervous system, lungs, liver, kidneys, systemic vasculature, coagulation, and the heart (1). Therefore, clinical manifestations of PE vary between individuals; some exhibit SPIP first in the absence of hypertension, so-called “isolated gestational proteinuria” (IGP), later developing hypertension and are then diagnosed with PE (8, 9). Therefore, IGP is proposed to be an early clinical sign of PE (10). Thus, there are three types of PE, i.e., IGP preceding PE in which IGP precedes hypertension, gestational hypertension (GH) preceding PE in which GH precedes SPIP, and PE in which hypertension and SPIP occur simultaneously (8,9,11). In a previous small single-center study (8), PE occurred in 19 of 37 IGP women (51%) approximately two weeks after the confirmation of IGP (8), thus suggesting that IGP was a prominent risk factor for PE. However, there have been no studies assessing how many women develop IGP, how many IGP women later develop hypertension, and what percentage of all PE cases are preceded by IGP. Addressing these issues may help to gain a better understanding of the nature of PE.

This multicenter retrospective observational study was conducted to determine the prevalence of IGP in singleton pregnancies and the proportion of women with IGP who subsequently developed preeclampsia (IGP-PE) among all PE cases.

Material and methods

This retrospective observational study was conducted after receiving approval from the Institutional Review Board of Hokkaido University Hospital (013-3999, April 30, 2014). The Japan Society of Obstetrics and Gynecology recommends 14 – 15 antenatal care visits before delivery and that pregnant women should undergo determination of blood pressure, proteinuria by dipstick test, and body weight at each visit (4). In this study, no definite protocols were predefined regarding the use of spot urine protein-to-creatinine ratio (P/Cr) test for confirmation of SPIP after obtaining dipstick test results. Therefore,

the performance of the P/Cr test was at the attending physician's discretion. However, in 2014, the Japan Society of Obstetrics and Gynecology recommended use of the P/Cr test with a threshold of 0.27 (mg/mg, corresponding to 30 mg/mmol) in women with the following dipstick test results: ≥ 1+ in the presence of hypertension, and ≥ 1+ on two successive antenatal care visits, and ≥ 2+ even in the absence of hypertension (4).

In this study, we abstracted the medical records of all 938 women with singleton pregnancies that underwent a P/Cr test at least once from a total of 6984 women (Fig. 1). The database provided by the institutional central laboratory of participating facilities helped to identify women who had a P/Cr test at least once. SPIP was defined as P/Cr > 0.27 (mg/mg, corresponding to 30 mg/mmol) in spot urine specimen (3,4,6,7,12 – 14), and IGP was defined as SPIP in the absence of hypertension. Hypertension was defined as the occurrence of systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and GH was defined as hypertension occurring on and after gestational week (GW) 20 in the absence of SPIP. PE was diagnosed in women who developed both hypertension and SPIP. Women with IGP or GH were followed-up once or more per week on an outpatient basis, and were admitted to one of the 12 participating hospitals when they were diagnosed as having PE. The GW at new onset of hypertension and SPIP was specified in each subject, and PE was classified into one of three types according to the timing of the onsets of hypertension and SPIP: simultaneous PE (S-PE) in which both hypertension and SPIP were confirmed on the same day, IGP preceding PE (IGP-PE) in which IGP occurred earlier than hypertension, and GH preceding PE (GH-PE) in which hypertension occurred earlier than SPIP.

In this study, no definite protocols were predefined regarding the use of induction of labor in PE patients. Therefore, PE patients were managed according to the policies at each institution. The Japan Society of Obstetrics and Gynecology recommends early delivery in PE women with one or more of the following conditions (4): uncontrollable hypertension exceeding systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 110 mmHg even with antihypertensive agents; net weight gain ≥ 3.0 kg per week; liver dysfunction as evidenced by elevated aspartate aminotransferase (> 45 IU/L) level and/or elevated level of lactate dehydrogenase (> 400 IU/L) concomitant with reduced platelet count (< 100×10^9/L) and/or reduced antithrombin activity level (< 60% of normal activity level); and an increase in proteinuria with P/Cr test result exceeding 5.0.

The following 12 facilities located throughout Japan participated in this study: Hiroshima University Hospital, Rakuwakai Otowa Hospital, Ohno Ladies Clinic, Mie Chuo Medical Center, Mie University Hospital, Nippon Medical School Tama Nagayama Hospital, Juntendo University Hospital, University of Tsukuba Hospital, Jichi Medical University Hospital, Fukushima Medical University Hospital, Hakodate Central General Hospital, and Hokkaido University Hospital. The clinical data, including patient age, parity, and clinical outcomes were obtained from medical charts of women with IGP, GH and PE.

Statistical analyses

Data are presented as median (range). Statistical analyses were performed using the JMP Pro11© statistical software package (SAS, Cary, NC). The Tukey–Kramer method was used for comparison of medians. Pearson's chi-square test was used for comparison of categorical variables. In all analyses, $p < 0.05$ was taken to indicate statistical significance.

Results

The flow of study participant is shown in figure 1. A total of 130 women were identified as having IGP, corresponding to 1.9% (130/6819) of the background pregnant population ($n = 6819$) (Fig. 1). Thirty-two (25%) of the 130 women with IGP later developed hypertension and were diagnosed with IGP-PE. GH-PE and S-PE were diagnosed in 77 and 49 of the 327 women included in the study population, respectively. Thus, IGP-PE women accounted for 20% (32/158) of all PE women. The total number of PE cases, i.e., 158, corresponded to 2.3% (158/6819) of the background population. Compared to 6689 women that were not diagnosed as having IGP, the risk of developing PE was significantly greater in the 130 women with IGP (25% [32/130] vs. 1.9% [126/6689], respectively, $p < 0.0001$) and the relative risk (95% confidence interval [CI]) of developing PE was 13.1 (95% CI; 9.2 – 18.5) for women with IGP.

The clinical characteristics were compared between groups (Table 1). Hypertension was diagnosed significantly earlier in the GH-PE group than the S-PE group. GW at the diagnosis of SPIP did not differ significantly between groups. The time interval between confirmation of SPIP and delivery was significantly longer in the IGP-PE group than in the other two PE groups. SPIP was confirmed postpartum for the first time in 15 of the 77 women (19%) with GH-PE. There were no significant differences in variables shown in Table 1 between 62 and 15 GH-PE women with SPIP confirmed ante- and postpartum, respectively, except for the GW at onset of hypertension (32.7 ± 4.0 vs. 35.1 ± 3.4, respectively, $p = 0.03$). Thus, GH-PE women with antepartum SPIP developed hypertension earlier compared to those with postpartum SPIP.

In this study, SPIP was diagnosed in women with P/Cr > 0.27. The P/Cr test was performed 96, 188, and 125 times for 32, 77, and 49 women diagnosed with IGP-PE, GH-PE, and S-PE, respectively (Table 2). The number of women with ≥ 3 P/Cr tests was significantly greater in the IGP-PE group than in the other two PE groups. There were no significant differences in protein concentration, creatinine concentration, or P/Cr level at diagnosis of SPIP between the three PE groups. However, the number of women with a P/Cr level > 1.0 at diagnosis of SPIP was significantly greater in the S-PE group than in the other two PE groups although GW at the diagnosis of SPIP did not differ significantly between groups; 67% (33/49) vs. 44% (14/32) with $p = 0.03$ for S-PE vs. IGP-PE, respectively and 67% [33/49] vs. 44% [34/77] with $p = 0.009$ for S-PE

vs. GH-PE, respectively (Table 2, Fig. 2B).

The P/Cr level appeared to increase with advancing gestational age in most patients with PE, although the rate of increase in P/Cr level (per unit time) varied greatly between individuals (Fig. 2A). Distribution of P/Cr level at the diagnosis of SPIP is shown in Fig. 2B.

Discussion

In this study, 1.9% (130/6819) of women with singleton pregnancies exhibited IGP defined as P/Cr level > 0.27 in the spot urine sample in the absence of hypertension, 25% (32/130) of IGP women later progressed to PE, and IGP-PE accounted for 20% (32/158) of all PE women. In a recent study by Samo et al. (15), IGP-PE accounted for 25% of all 195 PE women.

The gold standard for diagnosis of SPIP is proteinuria ≥300 mg in 24-hour urine (5 – 7), although PE can be diagnosed without confirmation of SPIP in hypertensive women with certain clinical conditions according to recent guidelines (5 – 7). We speculated that problems inherent in 24-hour urine collection may have prevented determination of the numbers of women exhibiting IGP, the numbers of women with IGP progressing to PE, and the percentage of IGP preceding PE in all cases of PE. To our knowledge, most guidelines (3, 5 – 7) for the diagnosis and treatment of hypertensive disorders in pregnancy do not mention the prevalence of IGP due to a lack of reports in the literature. This lack of reports may be due to difficulty in performing studies addressing these issues for several reasons. Convenient P/Cr testing using random urine samples has only recently been introduced in obstetric practice as an alternative to 24-hour urine collection (3 – 7). The rate of false positive test results on dipstick test is high due to the inherent nature of this primary screening tool for SPIP, especially in concentrated urine samples (16 - 19). Although 24-hour urine collection has been mandatory for diagnosis of SPIP, it is frequently incomplete and inconvenient for pregnant women (18 – 20); therefore, physicians may be reluctant to ask women for repeated 24-hour urine collection.

Our study design did not preclude the possibility that there may have been some women with IGP among the 5881 women that did not undergo P/Cr test at all during pregnancy (Fig. 1). However, it was notable that there were at least 130 IGP women, corresponding to 1.9% of the whole background population. In a recent study by Ekiz et al. defining SPIP as protein loss ≥ 300 mg in 24-hour urine samples (21), a much lower IGP prevalence rate of 0.5% (157/31 472) was reported. We speculate that this difference in IGP prevalence rate may have been due to difficulty in performing the 24-hour urine collection test. The P/Cr test was performed in 938 of all 6819 women (14%) (Fig. 1) and 409 times in the 158 PE women before and/or after the diagnosis of PE (Table 2) in this study.

The risk of PE among IGP women was 25% (32/130) in this study, which was relatively

consistent with that of 34% (53/157) in the study by Ekiz et al. (21). This clearly indicated that IGP is a risk factor for PE. The number of women diagnosed with PE in our setting corresponded to 2.3% of the whole background population of 6819 women, which was consistent with the results of a previous study in which the prevalence rate of PE based on traditional criteria for diagnosis was 2.3% among 301 735 pregnant Japanese women with singleton pregnancies (2). The risk of PE was estimated as 1.9% (128/6689) among women not diagnosed with IGP in this study, which was much lower than the rate of 25% among women with IGP, indicating a relative risk of 13.1 for developing PE in IGP women. Thus, IGP was an apparent prominent risk factor for PE in this study.

In this study, the number of women with a P/Cr level > 1.0 at diagnosis of SPIP was significantly greater in the S-PE group than in the other two PE groups (Table 2, Fig. 2B). Three previous studies (8, 9, 22) suggested that proteinuria increased with advancing gestational age. However, it was suggested that the rate of increase in proteinuria varied greatly between individuals in this study (Fig. 2A).

In conclusion, the present study demonstrated that IGP, defined as P/Cr > 0.27 (30 mg/mmol) in the absence of hypertension, is a risk factor for developing PE. IGP-PE accounts for a considerable proportion (20%) of all cases of PE. This knowledge may contribute to earlier diagnosis of PE and earlier delivery when indicated to improve outcomes in such women with IGP-PE.

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Figure Legends

Figure 1 Flow diagram of the study participants

GH, gestational hypertension; GH-PE, GH preceding preeclampsia (PE); GW, gestational week; IGP, isolated gestational proteinuria; IGP-PE, IGP preceding PE; SPIP, significant proteinuria in pregnancy (defined as P/Cr > 0.27); S-PE, simultaneous PE.

Shaded columns indicate 327 women who were abstracted from 6984 women after meeting all of the following four conditions: (1) singleton pregnancy, (2) new onset of SPIP or hypertension on and after GW 20, (3) no known renal diseases, and (4) no known hypertension. There were 6819 maternities carrying singletons at 12 centers during the 1-year study period between April 2014 and March 2015. The institutional central laboratory database identified 938 women with at least one P/Cr test, including 294 women with SPIP and 644 women without SPIP. The hospital discharge record database for the 644 women without SPIP identified 89 women with hypertensive disorders in pregnancy including chronic hypertension defined as hypertension confirmed before GW 20. The medical charts for each of the 294 women with SPIP and the 89 women with hypertension but without SPIP were reviewed. Gestational week at the new onset of SPIP and or hypertension was specified in the medical charts for each woman. Then, 56 women with known renal diseases, chronic hypertension, and or P/Cr > 0.27 before GW 20 were excluded.

Figure 2 Antenatal changes in P/Cr ratio (A) and P/Cr ratio at the diagnosis of SPIP (B)

A: The shaded area indicates P/Cr ratio < 0.27. Twenty-three of 32 women with IGP-PE, 28 of 77 women with GH-PE, and 21 of 49 women with S-PE underwent P/Cr test at least twice antepartum, and were shown to have SPIP antepartum (15 of the 77 women with GH-PE exhibited SPIP postpartum for the first time). The P/Cr ratio increased with advancing gestation in most PE patients, although the rate of increase of proteinuria varied greatly between individuals.

B: Distribution of P/Cr ratio at the diagnosis of SPIP is shown. Number of women with P/Cr > 1.0 is indicated in rectangles. A significantly greater number of women exhibited P/Cr > 1.0 at the diagnosis of SPIP in women with S-PE (67% [33/49]) than in those with IGP-PE (44% [14/32]) and GH-PE (44% [34/77]).

Figure 1

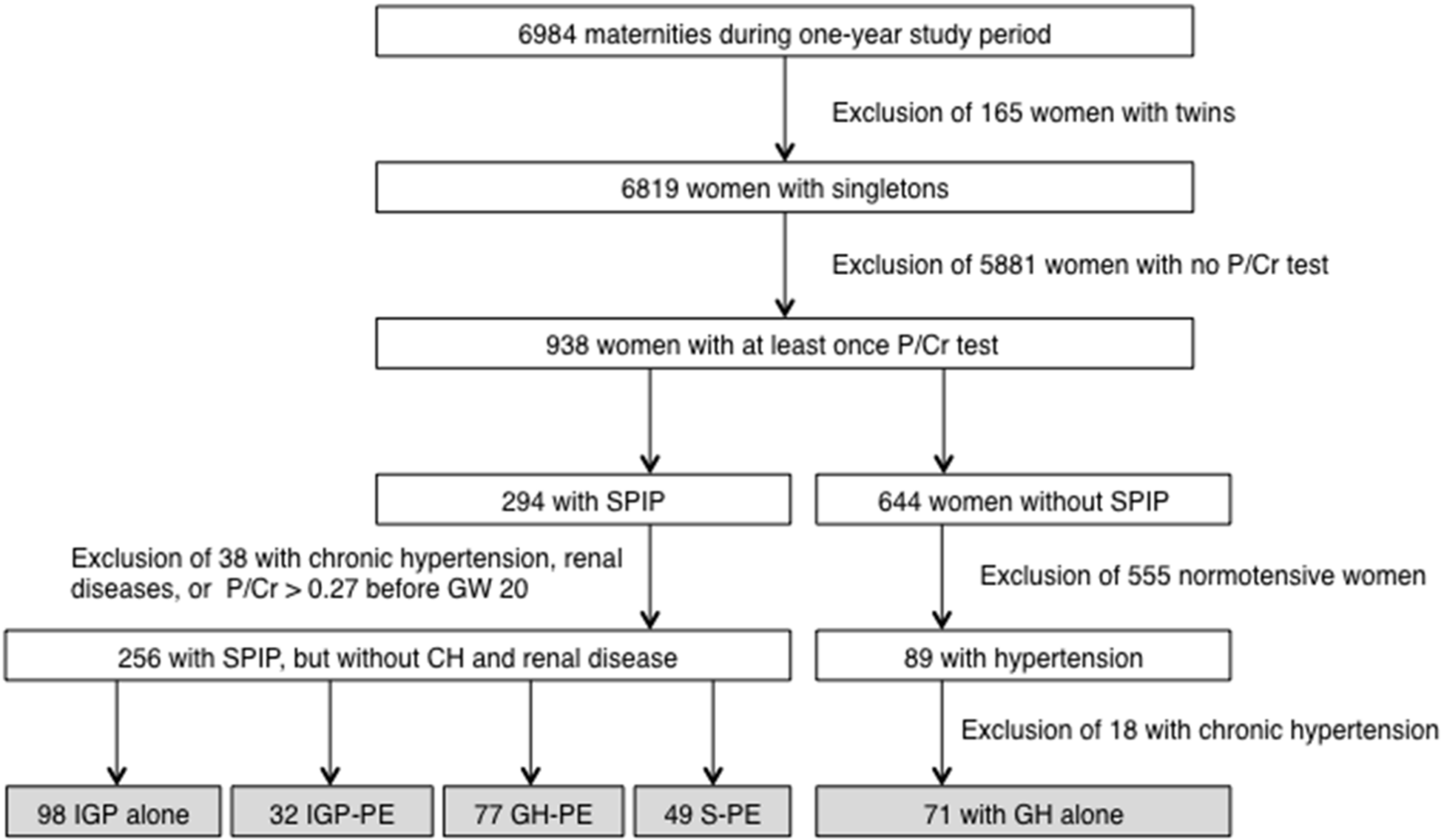

6984 maternities during one-year study period
Exclusion of 165 women with twins
6819 women with singletons
Exclusion of 5881 women with no P/Cr test
938 women with at least once P/Cr test
294 with SPIP
644 women without SPIP
Exclusion of 38 with chronic hypertension, renal diseases, or P/Cr > 0.27 before GW 20
Exclusion of 555 normotensive women
256 with SPIP, but without CH and renal disease
89 with hypertension
Exclusion of 18 with chronic hypertension
98 IGP alone
32 IGP-PE
77 GH-PE
49 S-PE
71 with GH alone

Figure 2

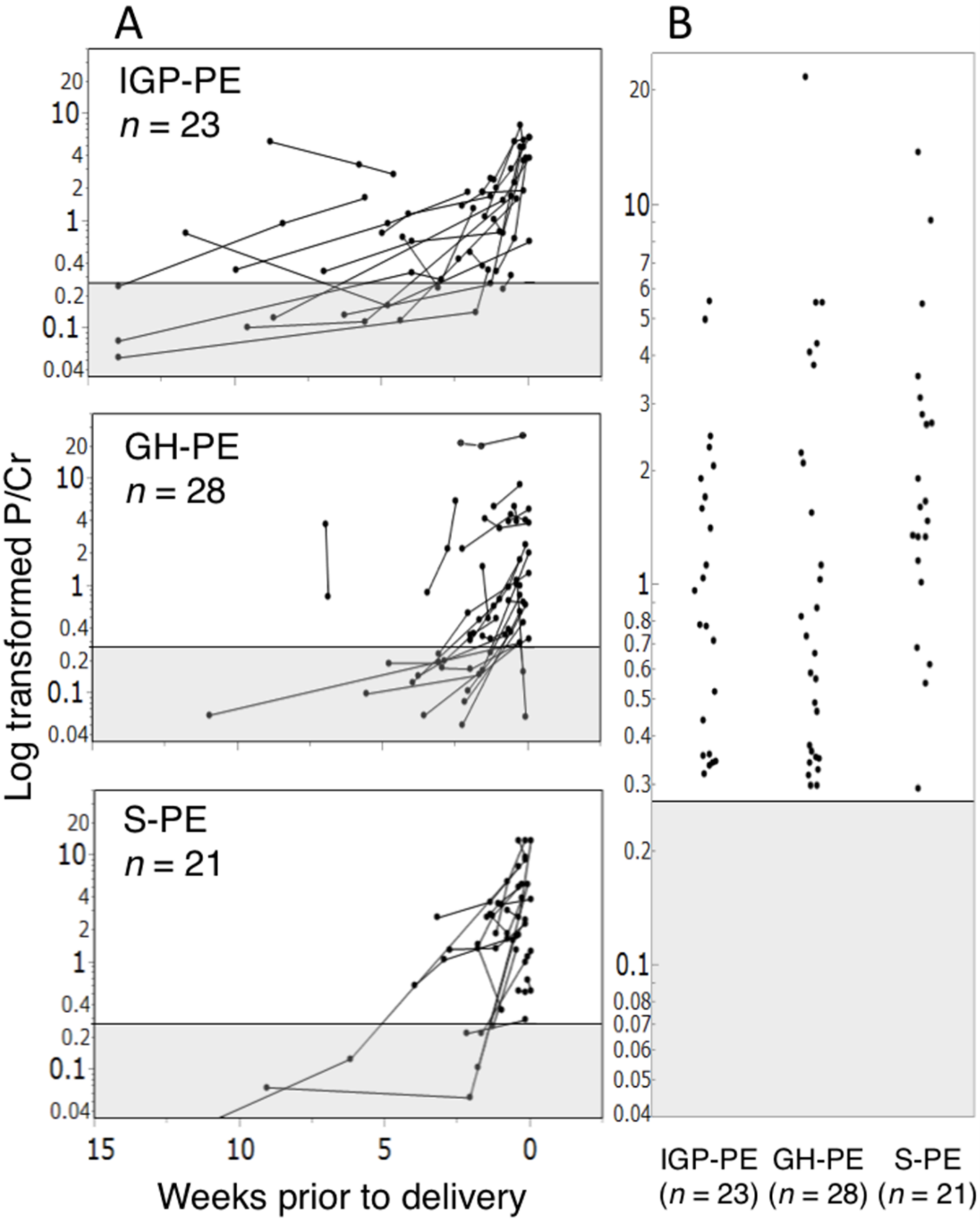

A
B
IGP-PE
n = 23
GH-PE
n = 28
S-PE
n = 21
Log transformed P/Cr
20
10
7
6
5
4
3
2
1
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.08
0.07
0.06
0.05
0.04
15
10
5
0
Weeks prior to delivery
IGP-PE (n = 23)
GH-PE (n = 28)
S-PE (n = 21)

Table 1 Demographic characteristics of 327 women

	IGP (n=130)		GH (n=148)		S-PE (n=49)
Final diagnosis	**IGP (n=98)**	**IGP-PE (n=32)**	**GH (n=71)**	**GH-PE (n=77)**	
Maternal age (yr)	31 (18-44)	33 (19-42)	34 (17-45)	35 (19-45)	34 (16- 41)
Nulliparous women	61 (62.2%)	23 (71.9%)	40 (56.3%)	46 (59.7%)[a]	37 (75.5%)[a]
GW at onset					
SPIP	35.0 (21.6–40.9)	33.3 (24.7-39.6)	NA	35.0 (23.9-PPW 0.9)	36.7 (23.6-41.1)
Hypertension	NA	36.0 (24.9-40.4)	35.9 (20.0-40.3)	33.7 (23.4-40.4)[a]	36.7 (23.6-41.1)[a]
Interval (weeks)‡	2.2 (-1.0 – 17.4)[a, b]	1.3 (0.2 – 11.7)[c, d]	NA	0.5 (0.0 – 7.0)[a, c]	0.3 (0.0 – 6.9)[b, d]
GW at delivery	38.8 (23.9-41.6)[a, b]	37.0 (25.3-40.7)	37.9 (27.0-41.6)[c]	36.4 (24.1-41.3) [a, c]	37.1 (23.7-41.3)[b]
< 37	20 (20.4%)[a, b]	16 (50.0%)[c]	19 (26.8%)[c, d, e]	44 (57.1%)[a, d]	22 (44.9%)[b, e]
Birth-weight (kg)	2.91 (0.62-3.98)[a, b, c]	2.20 (0.37-3.44)[a, d]	2.80 (0.67-4.01)[d, e]	2.15 (0.38-3.79)[b, e]	2.56 (0.44-4.06)[c]

Data are presented as the median (range) or number (percentage). ‡, Time interval until delivery after SPIP confirmation. Significant difference was compared between three groups including IGP-PE, GH-PE, and S-PE; $P < 0.05$ between two figures with superscript. GH, gestational hypertension; IGP, isolated gestational proteinuria; GW, gestational week; GH-PE, hypertension-preceding preeclampsia; IGP-PE, proteinuria-preceding preeclampsia; PPW, postpartum week; S-PE, simultaneous preeclampsia; SPIP, significant proteinuria in pregnancy. The 130 women with IGP developed SPIP at GW 34.9 (21.6–40.9) and 148 women with GH developed hypertension at GW 34.4 (20.0-40.4). SPIP was confirmed postpartum for the first time in 15 of the 77 women with GH-PE.

Table 2 P/Cr tests performed in three groups

	Final diagnosis		
	IGP-PE	GH-PE	S-PE
No. of women	32	77	49
Total no. of P/Cr tests	96	188	125
No. of P/Cr tests/person	3 (1 – 5) 2 (1 – 5)	2 (1 – 5)	
Once	6 (18.8%)	18 (23.4%)	14 (28.6%)
Twice	4 (12.5%)	23 (29.9%)	12 (24.5%)
Three times or more	22 (68.8%)[a]	36 (46.8%)[a]	23 (46.9%)
When SPIP was diagnosed			
[P] (mg/dL)	98 (10 – 683)	74 (9.1 – 3890)	158 (9.0 – 2396)
[Cr] (mg/dL)	122 (26 – 335)	91 (18 – 401)	119 (20 – 374)
P/Cr (mg/mg)	0.81 (0.32 – 5.6)	0.92 (0.27 – 21.7)	1.48(0.27 – 13.8)
< 0.5	9 (28.1%)	24 (31.2%)[a]	7 (14.3%)[a]
> 1.0	14 (43.8%)[a]	34 (44.2%)[b]	33 (67.4%)[a,b]
> 1.5	10 (31.3%)	27 (35.1%)	24 (49.0%)
> 2.0	6 (18.8%)	24 (31.2%)	19 (38.8%)
Dipstick test result			
Negative/equivocal	1 (3.1%)	13 (16.9%)	3 (6.1%)
1+	10 (31.3%)	20 (26.0%)	9 (18.4%)
≥ 2+	21 (65.6%)	44 (57.1%)[a]	37 (75.5%)[a]

Data are presented as the median (range) or number (percentage). [P], protein concentration; [Cr], creatinine concentration. $P < 0.05$ between two figures with superscript.