HOKKAIDO UNIVERSITY

Title	Plasma Aldosterone Concentration and Plasma Renin Activity Decrease during the Third Trimester in Women with Twin Pregnancies
Author(s)	Koyama, Takahiro; Yamada, Takashi; Furuta, Itsuko et al.
Citation	Hypertension in Pregnancy, 31(4), 419-426 https://doi.org/10.3109/10641955.2012.690057
Issue Date	2012-11
Doc URL	https://hdl.handle.net/2115/53469
Type	journal article
File Information	Hypertens Preqnancy_31(4)_419-426.pdf



Hokkaido University Collection of Scholarly and Academic Papers : HUSCAP

[ORIGINAL ARTICLE]

Plasma aldosterone concentration and plasma renin activity decrease during the third trimester in women with twin pregnancies

Takahiro KOYAMA, Takashi YAMADA,* Itsuko FURUTA, Mamoru MORIKAWA, Takahiro YAMADA, Hisanori MINAKAMI

Department of Obstetrics, Hokkaido University Graduate School of Medicine, Sapporo, Japan;

Disclosure: None of the authors have a conflict of interest.

Reprints: Takashi Yamada, MD, PhD, Department of Obstetrics, Hokkaido University Graduate School of Medicine, Kita-ku N14 W6, Sapporo 060-8638, Japan

TEL +81-11-706-6051 FAX +81-11-706-7981

E-mail address: yamataka@med.hokudai.ac.jp

Abstract

OBJECTIVE: Changes in the plasma aldosterone concentration (PAC) and the plasma renin activity (PRA) have not been extensively studied in women with twin pregnancies.

METHODS: The PAC and PRA levels were determined during the second and third trimesters and on postpartum day 3 in 14 normotensive women with twin pregnancies and 80 normotensive and 7 preeclamptic women with singleton pregnancies.

RESULTS: In women with twin pregnancies, elevated PAC and PRA levels (598 ± 248 pg/mL and 10.0 ± 4.7 ng/mL/hour, respectively) in the second trimester decreased significantly during the third trimester (to 396 ± 210 pg/mL and 3.5 ± 2.9 ng/mL/hour, respectively), while the corresponding PAC increased significantly from 421 ± 207 pg/mL to 667 ± 371 pg/mL and the PRA did not change significantly (from 7.3 ± 3.4 ng/mL/hour to 6.9 ± 4.2 ng/mL/hour) in women with normal singleton pregnancies. These changes in the PAC and PRA levels in women with twin pregnancies resembled those in hypertensive women with singleton pregnancies.

CONCLUSIONS: In women with twin pregnancies, both the PAC and PRA levels were significantly enhanced during the second trimester, while those in the third trimester were significantly reduced compared with those in women with normal singleton pregnancies.

(**Key words:** aldosterone, hypertension, preeclampsia, renin activity, twin pregnancy)

Introduction

Twin pregnancy differs considerably from singleton pregnancy in many aspects, such as the duration of pregnancy [11], the degree of enhancement of coagulation-fibrinolysis [14], the prevalence of pregnancy-induced hypertension [13, 9], and the degree of blood volume expansion [15]. All these data suggest that pregnancy-induced changes in various biological and physiological parameters may be greater in women with twin pregnancies than in women with singleton pregnancies.

In normal singleton pregnancies, the serum and urinary aldosterone levels are increased, reaching a maximum during the third trimester [2,10]. The plasma renin activity (PRA) is also increased during pregnancy, reportedly reaching a maximum at different stages of pregnancy partially because of differences in assay methods [10]: either at the end of the first trimester, followed by a sustained high level [7,10], or during the third trimester [2]. However, reductions in the plasma aldosterone concentration (PAC) and PRA occur temporally close to the clinical manifestation of preeclampsia in women with this condition [2,3,10].

As blood parameters such as the platelet count and antithrombin activity are likely to decrease [12,17] and creatinine, urate and aspartate aminotransferases are likely to increase before the development of hypertension in women with twin pregnancies [13], the changes in PAC and PRA may differ between women with twin and singleton pregnancies. Accordingly, we conducted this prospective study.

Methods

This study was conducted prospectively after being approved by the institutional review board at Hokkaido University Hospital. A total of 101 women, consisting of 14

women with twin pregnancies and 87 women with singleton pregnancies, provided their written informed consent to participate in this study and gave birth during the 24-month period between October 2008 and September 2010 at Hokkaido University Hospital. All the participants donated 10 mL of blood during the second (23 to 27 weeks) and/or third (30 to 37 weeks) trimesters and on postpartum day 3 to determine the plasma aldosterone concentration (PAC) and plasma renin activity (PRA). Of the 14 women with twin pregnancies, none developed hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) or proteinuria (≥ 0.3 g/day) while pregnant, but 7 of them transiently developed hypertension postpartum. All 87 women with singleton pregnancies were normotensive (systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg) before 20 weeks of gestation, but two women became hypertensive just before the first blood sampling during the second trimester and three and two other women developed hypertension before and after the second blood sampling performed during the third trimester, respectively. These seven women who developed hypertension and proteinuria during pregnancy were classified as hypertensive women with singleton pregnancies. The remaining 80 women were normotensive throughout pregnancy and the postpartum period (normal control women group).

All the women were allowed an unrestrained sodium diet. Venous blood was drawn into ethylenediamine tetraacetic acid (EDTA) Vacutainer tubes while the participants were in a seated position after they had been ambulatory. The plasma samples were processed at room temperature to avoid the cryoactivation of prorenin, and the samples were stored at -40°C until assayed. PRA was measured using a well-established radioimmunoassay kit (PRA [SRL]; Special Reference Laboratory Co., Tokyo)

according to the manufacturer's instructions. PAC was measured using a radioimmunoassay kit (Spac–S aldosterone; Dai-ichi Radioimmunoassay Laboratory Co., Tokyo) according to the manufacturer's instructions. Intra- and inter-assay coefficient variations were less than 11.0% for PRA and were less than 7.0% for PAC.

Statistical analyses were performed using the JMP8 statistical software package (SAS, Cary, NC). Differences in the means were tested using the Tukey-Kramer HSD (honestly significant difference) test between each group, and categorical variables were compared using the Fisher exact test. A P value of less than 0.05 was considered to indicate statistical significance.

Results

No statistically significant differences were seen in maternal age, pre-pregnancy body mass index, or body mass index between the three groups (Table 1). As two of the seven women with hypertensive singleton pregnancies gave birth at 24 and 25 weeks of gestation after the first blood sampling because of the worsening of preeclampsia and 3 of the 14 women with twin pregnancies gave birth before 30 weeks for reasons other than hypertensive disorders, the duration of pregnancy in these two groups was significantly shorter than that in women with normotensive singleton pregnancies.

In women with twin pregnancies, the mean PAC (pg/mL) of 598 ± 248 during the second trimester, which was significantly higher than that (421 ± 207) in women with normotensive singleton pregnancies (Table 2 and Fig. 1), decreased significantly to 396 ± 210 during the third trimester, while that of 421 ± 207 in women with normotensive singleton pregnancies increased significantly to 667 ± 371, leading to a reversal of the

PAC values between women with normotensive singleton pregnancies and those with twin pregnancies. In women with singleton pregnancies, the PAC was significantly lower in hypertensive women than in normotensive women during the third trimester. Nine out of 11 (82%) women with twin pregnancies and three out of four (75%) women with hypertensive singleton pregnancies who were examined longitudinally exhibited a decrease in PAC, while a significantly smaller percentage (21% [14/66], p=0.0005 vs. twin pregnancy) of women with normotensive singleton pregnancies exhibited a decrease in PAC (Fig. 1). The PAC decreased significantly on postpartum day 3 in all three groups.

In women with twin pregnancies, the mean PRA (ng/mL/hour) of 10.0 ± 4.7 during the second trimester, which was significantly higher than that (7.3 ± 3.4) in women with normotensive singleton pregnancies (Table 2 and Fig. 2), decreased significantly to 3.5 ± 2.9 during the third trimester and was significantly lower that that (6.9 ± 4.2) in women with normotensive singleton pregnancies and comparable to that (2.3 ± 1.6) in women with hypertensive singleton pregnancies. In women with singleton pregnancies, the PRA was significantly lower in hypertensive women than in normotensive women during the second and third trimesters. All 10 (100%) women with twin pregnancies and four (100%) hypertensive women with singleton pregnancies who were examined longitudinally exhibited a decrease in PRA, while a significantly smaller percentage (57% [32/66], p=0.0208 vs. twin pregnancy) of women with normotensive singleton pregnancies did so (Fig. 2). The PRA decreased significantly on postpartum day 3 in all three groups.

The PAC-to-PRA ratio increased significantly with advancing gestation in both women with normotensive singleton pregnancies and those with twin pregnancies

(Table 2 and Fig. 3).

Discussion

This study demonstrated that both the PAC and PRA levels in women with twin pregnancies were significantly enhanced during the second trimester but significantly reduced during the third trimester, compared with those in normotensive women with singleton pregnancies. Reduced PAC and PRA levels were also confirmed in hypertensive women with singleton pregnancies, consistent with previous results [2,3,10].

During normal pregnancy, the renin-angiotensin-aldosterone system is thought to play a vitally important role in salt balance. Preeclampsia is thought to occur as a result of a derangement in this delicate equilibrium [8], although the precise mechanisms leading to the development of preeclampsia remain unknown. For example, PRA is suppressed in women with preeclampsia compared with that in normotensive pregnant women [2,3,10], as was also shown in this study, and a longitudinal study demonstrated that a low PRA of < 4.0 ng/mL/hour at 20 weeks of gestation can predict the development of superimposed preeclampsia among women with chronic hypertension [1]. Thus, a reduced PRA is consistently associated with the development of hypertensive disorders in pregnancy.

Escher and Mohaupt [5] insisted that “As high aldosterone levels are required during normal pregnancy to increase the circulating plasma volume as an adaptative mechanism to support placental perfusion, a diminished aldosterone production attributed to genetic predisposition or exogenous factors would abrogate the pregnancy-associated expansion of circulating fluid volume in preeclampsia.” The

circulating blood volume is markedly reduced in women with preeclampsia and eclampsia [16,19], and this phenomenon may be explained partly by insufficient aldosterone production [5] based on the following findings: 1) serum and urinary aldosterone is suppressed in women with preeclampsia [2-4,10], as was also shown in this study; 2) urinary aldosterone (tetrahydro-aldosterone) is inversely correlated with blood pressure during pregnancy [4]; and 3) supplemental NaCl administration during pregnancy was useful for reducing the blood pressure to within a normal range in a woman with a genetic predisposition to insufficient aldosterone production [6], suggesting that a sufficient and adequate blood volume determined primarily by the PAC prevents the development of preeclampsia. Thus, the suppression of PAC, compared with that in normotensive women, is a characteristic feature of women who develop preeclampsia and may be responsible for the development of preeclampsia.

In this study, women with twin pregnancies exhibited enhanced PAC and PRA levels during the second trimester and reduced PAC and PRA levels during the third trimester. To the best of our knowledge, no previous reports have dealt with this issue in women with twin pregnancies. The normal maternal blood volume expansion is greater in women with twin pregnancies than in those with singleton pregnancies [15]. According to the theory proposed by Escher and Mohaupt [5], women with twin pregnancies require a higher PAC than women with singleton pregnancies. The higher PAC during the second trimester seen in the women with twin pregnancies may reflect the above situation. Women with twin pregnancies are more likely to develop hypertensive disorders, such as gestational hypertension, preeclampsia, and eclampsia, than women with singleton pregnancies [9,13]. Although the present 14 women with twin pregnancies did not develop hypertension during pregnancy, seven (50.0%) of the

14 women developed hypertension postpartum, consistent with the results of a recent study in which 60 (40%) of 150 women with twin pregnancies developed postpartum hypertension [13]. Thus, women with twin pregnancies are prone to the development of hypertension. The significant decreases in PAC and PRA seen in women with twin pregnancies, resembling those reported in women with preeclampsia [2,3,10], maybe responsible for the likelihood of hypertension in women with twin pregnancies.

Although not confirmed in this study (Table 2), the PAC-to-PRA ratio is reportedly higher in women with preeclampsia than in normotensive women because of the relatively smaller decrease in PAC than in PRA in women with preeclampsia [3]. Although the difference did not reach a significant level, the PAC-to-PRA ratio of the women with twin pregnancies appeared to be higher than that of normotensive women with singleton pregnancies and resembled that of hypertensive women with singleton pregnancies. Of the 10 women with twin pregnancies who were examined for both PAC and PRA longitudinally, 7 women developed postpartum hypertension and 3 did not. In the sub-analysis of these 10 women, the 7 women with postpartum hypertension exhibited PAC-to-PRA ratios of 69.4 ± 29.2 and 188.5 ± 172.2 pg/ml per ng/ml/hour during second and third trimester, respectively, while corresponding those were 56.8 ± 22.5 and 106.0 ± 47.3 pg/ml per ng/ml/hour in the 3 women without postpartum hypertension. Thus, a large increase in the PAC-to-PRA ratio appeared to precede the development of postpartum hypertension in the 7 women. A high PAC-to-PRA ratio ≥ 200 pg/ml per ng/ml/hour is known to occur in patients with primary aldosteronism [18]. However, the mechanisms producing a higher PAC-to-PRA ratio in women with preeclampsia are poorly understood [3].

In conclusion, a higher PAC and a higher PRA during the second trimester of

women with twin pregnancies decreased sharply during the third trimester in the absence of hypertension. These changes in PAC and PRA differed considerably from those in normotensive women with singleton pregnancies but resembled those in hypertensive women with singleton pregnancies.

References

[1] August P, Helseth G, Cook EF, Sison C. A prediction model for superimposed preeclampsia in women with chronic hypertension during pregnancy. Am J Obstet Gynecol 2004; 191: 1666-72.

[2] August P, Lenz T, Ales KL, Druzin ML. Edersheim TG, Hutson JM, et al. Longitudinal study of the renin-angiotensin-aldosterone system in hypertensive pregnant women: deviations related to the development of superimposed preeclampsia. Am J Obstet Gynecol 1990; 163: 1612-21.

[3] Brown MA, Wang J, Whitworth JA. The renin-angiotensin-aldosterone system in pre-eclampsia. Clin Exper Hypertens 1997; 19; 713-26.

[4] Escher G, Cristiano M, Causevic M, Baumann M, Frey FJ, Surbek D, Mohaupt MG. High aldosterone-to-renin variants of *CYP11B2* and pregnancy outcome. Nephrol Dial Transplant 2009; 24: 1870-5.

[5] Escher G, Mohaupt M. Role of aldosterone availability in preeclampsia. Mol Aspects Med 2007; 28: 245-54.

[6] Farese S, Shojaati K, Kadereit B, Frey FJ, Mohaupt MG. Blood pressure reduction in pregnancy by sodium chloride. Nephrol Dial Transplant 2006; 21: 1984-7.

[7] Hsueh WA, Luetscher JA, Carlson EJ, Grislis G, Fraze E McHargue A. Changes in active and inactive renin throughout pregnancy. J Clin Endocrinol Metab 1982; 192; 54: 1010-6.

[8] Irani RA and Xia Y. The functional role of the renin-angiotensin system in pregnancy and preeclampsia. Placenta 2008; 29: 763-71.

[9] Krotz S, Fajardo J, Ghandi S, Patel A, Keith LG. Hypertensive disease in twin pregnancies: a review. Twin Res 2002; 5: 8-14

[10] Langer B, Grima M, Coquard C, Bader A-M, Schlaeder G, Imbs J-L. Plasma active renin, angiotensin I, and angiotensin II during pregnancy and in preeclampsia. Obstet Gynecol 1998; 91: 196-202.

[11] Minakami H, Sato I. Reestimating date of delivery in multifetal pregnancies. JAMA 1996; 275: 1432-4.

[12] Minakami H, Watanabe T, Izumi A, Matsubara S, Koike T, Sayama M, Moriyama I, Sato I: Association of a decrease in antithrombin III activity with a perinatal elevation in aspartate aminotransferase in women with twin pregnancies: relevance to the HELLP syndrome. J Hepatol. 1999; 30: 603-611.

[13] Morikawa M, Cho K, Yamada T, Yamada T, Akaishi R, Koyama T, Takeda M, Nichida R, Minakami H. Risk factors for postpartum hypertension in women with twin pregnancies. J Perinat Med, 2011 Oct 23. [Epub ahead of print], PMID: 22017329

[14] Morikawa M, Yamada T, Yamada T, Akaishi R, Koyama T, Minaakami H. Changes in D-dimer levels after cesarean section in women with singleton and twin pregnancies. Thromb Res. 2011 Oct;128(4):e33-8. Epub 2011 Jun 8.

[15] Pritchard JA. Changes in blood volume during pregnancy. Anesthesiology 1965; 26:393-9.

[16] Silver HM, Seebeck MA, Carlson R: Comparison of total blood volume in normal, preeclamptic, and nonproteinuric gestational hypertensive pregnancy by simultaneous measurement of red blood cell and plasma volumes. Am J Obstet Gynecol 1998; 179: 87-93.

[17] Tsunoda T, Ohkuchi A, Izumi A, Watanabe T, Matsubara S, Sato I, Minakami H: Antithrombin III activity and platelet count are more likely to decrease in twin

pregnancies than in singleton pregnancies. Acta Obstet Gynecol Scand 2002; 81: 840-845.

[18] Young WF. Primary aldosteronism: renaissance of a syndrome. Clin Endocr 2007; 66: 607-18.

[19] Zeeman GG, Cunningham FG, Pritchard JA. Hypertens Preg 2009; 28: 127-37.

Figure legends

Figure 1: Changes in plasma aldosterone concentration (PAC). Eleven of the 14 women with twin pregnancies, four of the seven hypertensive women with singleton pregnancies, and 66 of the 80 normotensive women with singleton pregnancies were examined twice during pregnancy.

Figure 2: Changes in plasma renin activity (PRA). Ten of the 14 women with twin pregnancies, four of the seven hypertensive women with singleton pregnancies, and 56 of the 80 normotensive women with singleton pregnancies were examined twice during pregnancy.

Figure 3: Changes in PAC-to-PRA ratio. Ten of the 14 women with twin pregnancies, four of the seven hypertensive women with singleton pregnancies, and 56 of the 80 normotensive women with singleton pregnancies were examined twice during pregnancy.

Table 1. Demographic characteristics

	Twin	Singleton	
		Hypertensive	Normotensive
Number of women	14	7	80
Maternal age (years old)	31.1±4.2	35.0±5.3	32.6±5.0
Pre-pregnant BMI (kg/m^2)	21.6±2.3	25.4±8.7	21.9±4.6
BMI at delivery (kg/m^2)	26.0±2.7	29.1±7.1	25.8±4.5
Gestational week at delivery	34.8±3.8*	32.0±5.9*	38.0±2.1
Sum of birth weight (g)	3990±1308*	1662±1070*	2900±453
Systolic blood pressure (mmHg)	115±14	161±18*	108±11
Diastolic blood pressure (mmHg)	65±13	90±9*	63±9
Proteinuria (g/day)	-	3.8±3.5	-

Data are shown as mean±SD; BMI,body mass index; *;$p<0.0001$ vs normotensive singleton pregnancies

Table 2. Changes in aldosterone and plasma renin activity in three groups

	Twin	Singleton	
		Hypertensive	Normotensive
Number of women	14	7	80
PAC (pg/ml)			
2nd trimester	598±248* n=14 (24.9±1.2)	329±207 n=6 (24.7±1.5)	421±207 n=70 (24.7±0.9)
3rd trimester	396±210†* n=11 (34.7±0.8)	303±218* n=5 (33.2±2.2)	667±371† n=76 (35.4±1.1)
Postpartum day 3	54±20†* n=13	58±59† n=7	99±72† n=73
PRA (ng/ml/hour)			
2nd trimester	10.00±4.71* n=13 (24.8±1.2)	3.6±2.0* n=6 (24.7±1.5)	7.3±3.4 n=68 (24.7±0.9)
3rd trimester	3.50±2.89†* n=11 (34.7±0.8)	2.3±1.5* n=5 (33.2±2.2)	6.9±4.2 n=68 (35.5±1.1)
Postpartum day 3	0.92±0.42† n=11	0.97±0.37† n=7	1.2±0.69† n=72
PAC-to-PRA ratio (pg/ml per ng/ml/hour)			
2nd trimester	65.8±25.9 n=13 (24.8±1.2)	84.3±27.8 n=6 (24.7±1.5)	63.6±28.3 n=68 (24.7±0.9)
3rd trimester	154.4±143.6 † n=11 (34.7±0.8)	149.0±109.3 n=5 (33.2±2.2)	114.7±51.1† n=68 (35.5±1.1)
Postpartum day 3	68.3±39.2 n=11	81.3±105.4 n=7	99.1±53.7 n=72

Data are shown as mean±SD. Gestational week at examination was presented in parenthesis.

PAC, plasma aldosterone concentration; PRA, plasma renin activity; *,$p<0.05$ vs normotensive singleton pregnancies; , †,$p<0.05$ vs value of 2nd trimester.

Fig. 1 Koyama *et al.*

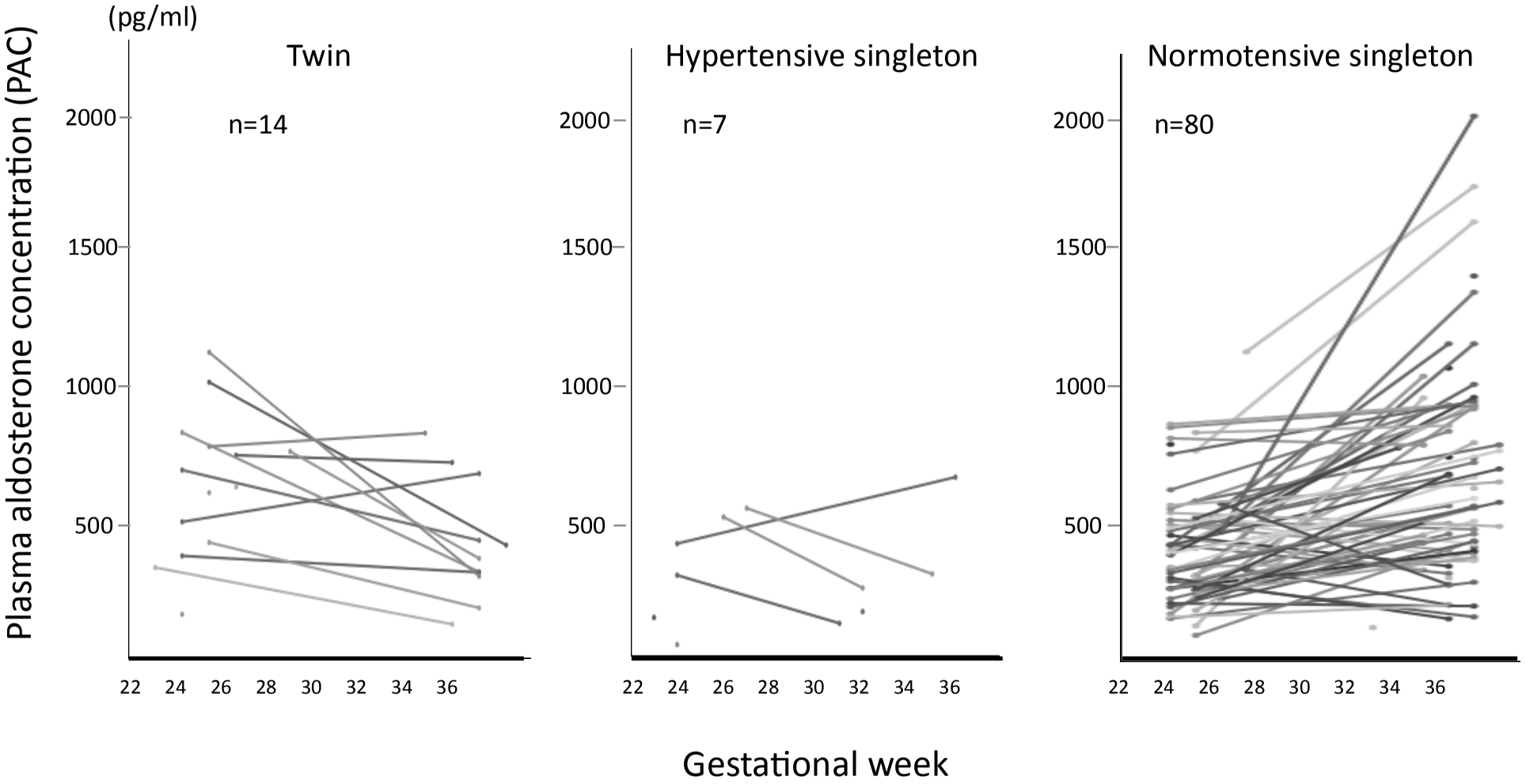


Fig. 2 Koyama *et al.*

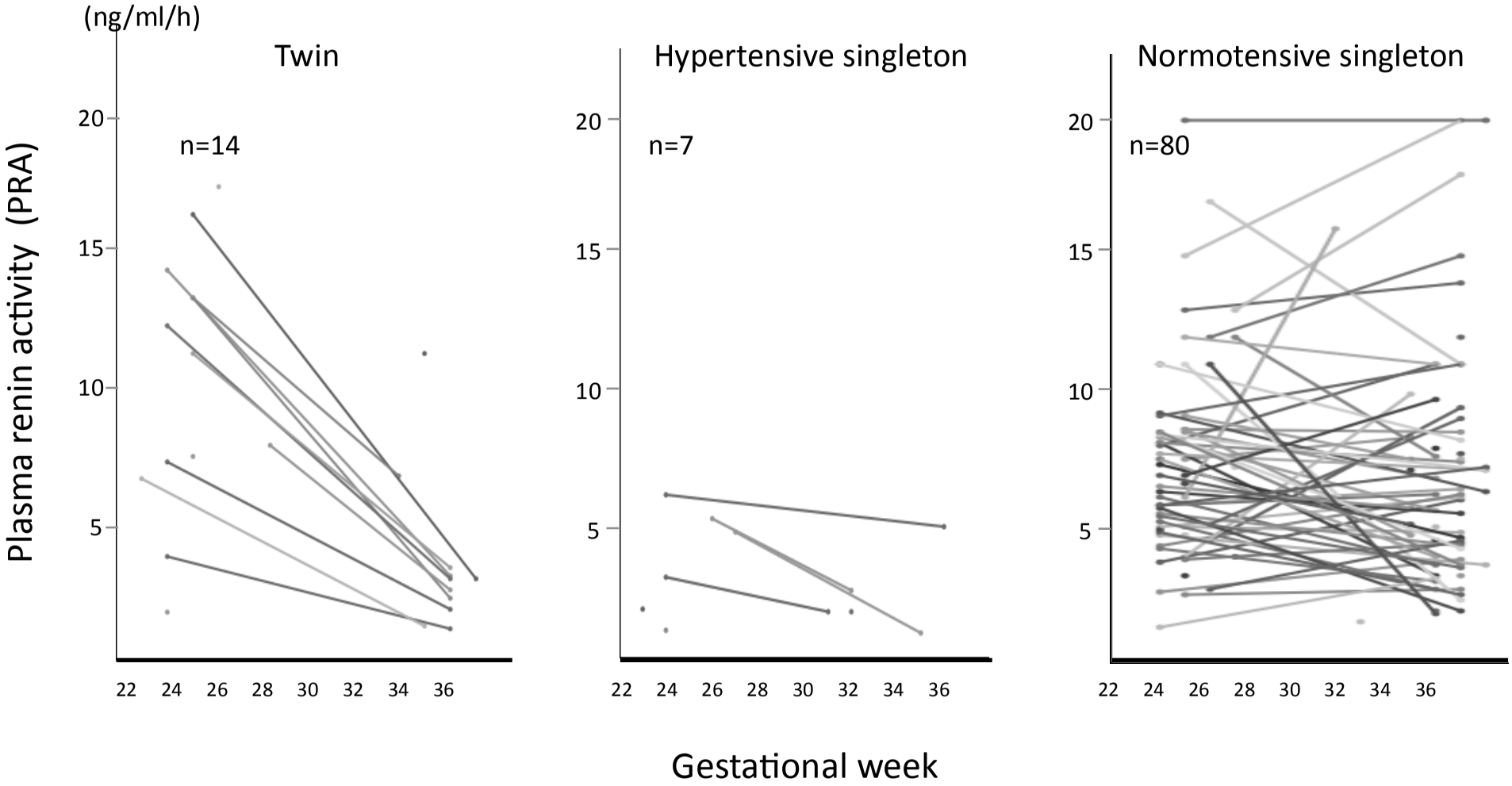


Fig. 3 Koyama *et al.*

