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Twin pregnancies can aggravate maternal renal function in late pregnancy compared to singleton pregnancies: a retrospective study

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Abstract

Objective: This study aimed to evaluate the differences in maternal renal function between singleton and twin pregnancies in the second half of pregnancy. Design: Retrospective study Setting: Japanese Red Cross Aichi Medical Center Nagoya Daiichi Hospital from January 2019 to June 2021. Population: This study included 1711 pregnant women with 1547 singleton pregnancies and 164 twin pregnancies. Methods: Patients underwent renal function tests (serum blood urea nitrogen, creatinine, and estimated glomerular filtration rate [eGFR]) at least one month prior to delivery. Main Outcome Measure: Maternal renal dysfunction, defined as serum creatinine of above 0.8 mg/dL. Results: Serum creatinine level was significantly higher and eGFR was significantly lower in twin pregnancies than that in singleton pregnancies ($p < 0.001$). In addition, the rate of renal dysfunction was significantly higher in twin than that in singleton pregnancies (7.9% vs. 2.6%; $p < 0.001$). Multivariate analysis revealed that twin pregnancy (odds ratio [OR] 3.38), nulliparity (OR 2.31), and preeclampsia (OR 3.64) were significant risk factors for maternal renal dysfunction. Maternal renal dysfunction was observed in 13 twin pregnancies, all of which recovered to within normal limits during the postpartum period. Conclusions: Twin pregnancy is a significant risk factor for maternal renal dysfunction. Careful attention should be paid to maternal renal dysfunction in the management of twin pregnancies. Funding: Japanese Red Cross, Nagoya Daiichi Hospital Research Grant (grant number NFRCH22-0011). Keywords: chorionicity, renal function, serum creatinine concentration, singleton pregnancy, twin pregnancy

Introduction

Pregnancy causes structural and functional changes in maternal kidneys. The length of both kidneys increases by 1 to 1.5 cm during pregnancy[1], and kidney volume increases by up to 30%[2]. Pregnancy also leads to increased renal plasma flow (RPF) and glomerular filtration rate (GFR)[3]. The physiological increase in GFR during pregnancy decreases serum creatinine concentrations during early pregnancy[4]. In a retrospective database study in Canada, the mean serum creatinine concentration decreased in the first trimester of pregnancy, leveled off in the second, and then gradually increased again in the third trimester to near pre-pregnancy levels[5]. Thus, a serum creatinine of 0.8 mg/dL (70.7 μmol/L) or higher, which may be normal in non-pregnant women, usually reflects renal impairment in pregnant women, and a slight increase in serum creatinine usually reflects a significant decrease in renal function. Therefore, to detect renal impairment during pregnancy, it is necessary to note even mild variation in serum creatinine levels.

The increase in GFR during gestation is primarily due to an increase in RPF[6]. RPF increases by up to 80% at 12 weeks of gestation[7]but decreases in the third trimester. Increased renal blood flow and GFR are caused by changes in the quantity of systemic blood flow (increased cardiac output) and systemic vasodilation[8]. Systemic vasodilation is induced mainly by the renin-angiotensin-aldosterone system (Angiotensin-1 receptors, causing vasoconstriction are down regulated, angiotensin-2 receptors, causing vasodilation are upregulated, and the levels of angiotensin-2 and aldosterone are increased)[9], and progesterone, nitric oxide, and relaxin have been reported to play an important role in the hemodynamic changes in kidney function during

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pregnancy[8-11]. However, RPF begins to decrease in the second trimester and rapidly falls in the third trimester[8,12]. In addition, filtration fraction and proteinuria increase after 20 weeks of gestation[8,13]. Furthermore, an enlarged uterus negatively affects renal function by compression of the inferior vena cava (IVC), leading to decreased cardiac output, compression of the renal vein, and impaired ureteral transit due to ureteral dilation in the second half of pregnancy. These conditions can aggravate maternal renal dysfunction.

In this study we speculate that the effects of pregnancy on maternal renal function can differ between singleton and multiple pregnancies. However, to the best of our knowledge, no relevant scientific report investigating this hypothesis has been published. The purpose of this study was to examine the differences in maternal renal function between singleton and twin pregnancies in the second half of pregnancy.

Methods

Participants

This was a retrospective study of 2676 deliveries at our institution from January 2019 to June 2021. In our hospital, when a cesarean section was necessary (or is considered highly likely), we performed blood tests (complete blood counts, biochemical tests including kidney and liver function, coagulation tests, and tests for infectious diseases including HIV), chest radiography, and electrocardiography as preoperative tests, within at least one month of delivery. All twin pregnancies underwent preoperative examinations. After excluding 965 patients (including 959 cases in which blood tests were not performed, three cases of missing data, and three cases of triplet pregnancy), we finally enrolled 1711 patients pregnant with 1547 singleton pregnancies and 164 twin pregnancies who underwent renal function tests (serum blood urea nitrogen [BUN], creatinine, and estimated glomerular filtration rate [eGFR]) within at least one month of delivery (Supplementary Figure 1). The study conformed to the principles outlined in the Declaration of Helsinki of 1964. This study was approved by the Ethics Committee of the Japanese Red Cross Nagoya Daiichi Hospital, Nagoya, Japan (approval number: 2021-422).

Case selection and definition

We assessed blood pressure, and performed urinalysis and ultrasound, including fetal position, fetal growth, and amniotic fluid volume at each examination, screening for congenital anomalies, when needed. All maternal and ultrasound data were stored in medical records. In twin pregnancies, ultrasound was performed in the first trimester to determine chorionicity and amnionicity. That is, an intertwin membrane with the "twin peak" or "lambda" sign indicates dichorionic twins, and an intertwin membrane with the "T" sign indicates monochorionic twins[14]. Maternal renal dysfunction was defined as a serum creatinine of above 0.8 mg/dL. Preeclampsia was defined as the occurrence of gestational hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg after 20 weeks of gestation), proteinuria (>300 mg on 24-hour urine collection), and/or signs of end-organ dysfunction during pregnancy[15]. Fetal growth restriction was defined as a birth body weight of <-1.5 SD for gestational age in Japan[16].

Statistical analyses

Clinical data were extracted from medical records and entered into a computerized spreadsheet (Excel, Microsoft Japan Co., Ltd., Tokyo, Japan). EZR software (version 1.38, Saitama, Japan) was used to perform all data analyses. After using the Shapiro-Wilk test to assess the normality of the data, the Mann–Whitney U test was conducted to compare continuous variables between the two groups, and the Student's t -test was used where appropriate. The chi-square test was used to compare the following categorical variables: nulliparity, diabetes mellitus, preeclampsia, fetal growth restriction, and maternal renal dysfunction. Continuous variables included maternal age, body mass index, birth weight, gestational age at blood test, serum BUN, creatinine, and eGFR. A logistic regression model that included maternal age, body mass index, nulliparity, gestational age at blood test, twin pregnancy, diabetes mellitus, preeclampsia, and fetal growth restriction was used to develop the prediction model for maternal renal dysfunction. For each variable, odds ratios and 95% confidence intervals (95% CI) were estimated. Statistical significance set at $p < 0.05$ were considered

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statistically significant.

Results

Maternal characteristics and renal function between singleton and twin pregnancies

Maternal characteristics are shown in Table 1. In this study, maternal age, pre-pregnancy body mass index, and nulliparity rate were not significantly different between singleton and twin pregnancies. However, the rate of fetal growth restriction was significantly higher in twin pregnancies than that in singleton pregnancies ($p < 0.001$). A comparison of maternal renal function between singleton and twin pregnancies is presented in Table 2. The gestational age at blood test were significantly earlier in twin pregnancies than that in singleton pregnancies ($p < 0.001$). Serum creatinine level was significantly higher and eGFR was significantly lower in twin pregnancies than that in singleton pregnancies ($p < 0.001$). In addition, the rate of renal dysfunction was significantly higher in twin than that in singleton pregnancies (7.9% vs. 2.6%; $p < 0.001$).

Risk factors for maternal renal dysfunction using multivariate logistic regression analysis

The multivariate analysis results for the risk of maternal renal dysfunction are shown in Table 3. In multivariate analysis, maternal age, body mass index, nulliparity, gestational age at blood test, twin pregnancy, diabetes mellitus, preeclampsia, and fetal growth restriction were included as variables to calculate the odds ratio (OR) for maternal renal dysfunction. Twin pregnancy (OR 3.38), nulliparity (OR 2.31), and preeclampsia (OR 3.64) were significant risk factors for maternal renal dysfunction.

Renal function between dichorionic and monochorionic twin pregnancy

Renal function during pregnancy between dichorionic and monochorionic twin pregnancies is shown in Table 4. Serum creatinine level was significantly higher and eGFR was significantly lower in dichorionic twins ($p < 0.05$); however, the mean values were within the normal range. Maternal renal dysfunction was observed in 13 twin pregnancies: 10 (9.1%) dichorionic twins and three (5.8%) monochorionic twins, and the rate of maternal renal dysfunction was not significantly different between dichorionic and monochorionic twins ($p = 0.552$).

Prognosis in cases of maternal renal dysfunction in twin pregnancy

As described above, maternal renal dysfunction was observed in 13 twin pregnancies in the present study. In 10 of these cases, renal function normalized within one month postpartum. In the remaining three cases, renal function also normalized within three months postpartum without medical intervention (two within two months postpartum and the other within three months postpartum).

Discussion

Main Findings

Multivariate analysis showed that twin pregnancy, nulliparity, and preeclampsia were significantly associated with maternal renal dysfunction during pregnancy. Although preeclampsia is clearly associated with maternal renal dysfunction, the present study revealed that twin pregnancy is a risk factor for maternal renal dysfunction. However, there were no differences in maternal renal function based on chorionicity. In the present study, all 13 twin mothers with renal dysfunction recovered to within normal limits during the postpartum period.

Interpretation

Pregnancy causes structural and functional changes in maternal kidneys. During the first half of pregnancy, maternal cardiac output, RPF, and GFR increase and systemic vascular resistance decreases; as a result, the mean serum creatinine concentration is lower than that of non-pregnant women[4,7,8]. Several mechanisms have been reported to contribute to decreased vascular resistance. During pregnancy, vascular expression of angiotensin-2 receptors, which causes vasodilation rather than vasoconstriction in response to angiotensin-2, increases[17]. During normal pregnancy, nitric oxide synthesis increases, which contributes to systemic and

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renal vasodilation[10]. Relaxin, which is secreted in large amounts by the placenta and decidua in response to human gonadotropin during pregnancy, increases endothelin and nitric oxide production in the renal circulation, leading to generalized renal vasodilation, decreased renal afferent and efferent arteriole resistance, and a subsequent increase in renal blood flow and GFR[18]. Conversely, during the second half of pregnancy, RPF decreases slightly, resulting in an increased filtration fraction and proteinuria[8,12,19,20]. However, not all studies support an increase in the filtration fraction during the third trimester of pregnancy, and the mechanisms that drive the physiological increase in urinary protein excretion during pregnancy are not well-understood. In addition, physical pressure on the blood vessels and organs by the pregnant uterus occurs, especially during the late pregnancy period. This may have a negative effect on the maternal renal function.

This is the first study, to the best of our knowledge, to show that twin pregnancy itself is a significant factor associated with maternal renal dysfunction during the latter half of pregnancy. Below, we discuss how twin pregnancies can cause maternal renal dysfunction. First, the cardiac output of women with twin pregnancies is 20% higher than that in singleton pregnancies, and peaks at 30 weeks of gestation[21]. On the other hand, compared with the left lateral decubitus position, the supine position can lower cardiac output by as much as 25–30% due to compression of the IVC by the gravid uterus[22]. Therefore, because of the larger uterus in twin pregnancies compared to singleton pregnancies, the longer the patient is in the supine position, the highly pronounced IVC compression is likely to result in a greater reduction in cardiac output and thus RPF. Decreased RPF can result in decreased GFR. However, there were no data on the posture of the pregnant women in this study, and future studies are needed to investigate this aspect.

Second, hydroureter and hydronephrosis occurs in approximately 80% of pregnant women and is more pronounced on the right side than on the left[23]. Hydroureters and hydronephrosis during pregnancy have been attributed to hormonal influences, external compression, and intrinsic changes in the ureteral wall[24]. Progesterone reduces ureteral tone, peristalsis, and contraction pressure, which are further increased in twin pregnancies. As pregnancy advances, an enlarged uterus may cause the ureters to become elongated, tortuous, and laterally displaced. As mentioned above, twin pregnancies are more prominent than singleton pregnancies because of urinary tract compression. Occasionally, obstruction of the ureters by the uterus is sufficient to cause kidney failure[25]. Acute kidney injury due to urinary obstruction resulting from enlarged uterine fibroids during pregnancy has been reported[26], which can be resolved by insertion of a ureteric stent or delivery of the fetus[27]. In summary, we can assume that twin pregnancies are more likely to cause urinary tract obstruction and, therefore, maternal renal dysfunction. Third, during pregnancy, especially in the third trimester, proteinuria increases, and the rate of pathological proteinuria (300 mg/day or greater) is greater in twin pregnancies than that in singleton pregnancies (adjusted OR = 9.13)[20]. In recent years, the usefulness of the urine albumin-to-creatinine ratio (UACR) has been introduced, which is strongly predictive of significant proteinuria. The diagnostic accuracy of the UACR (using a threshold between 20 and 60 mg albumin/g creatinine) and the urine protein-to-creatinine ratio (UPCR) (>300 mg protein/day by 24-hour urine collection) are approximately equal, and the UACR is increasingly being replaced by UPCR[28-30]. Increased albuminuria reflects the impaired permselectivity of glomerular capillaries to macromolecules, which is reported to be a marker of kidney damage[31]. This suggests that an increase in proteinuria (albuminuria) due to twin pregnancies causes kidney damage, resulting in renal dysfunction. Unfortunately, we have no data regarding proteinuria (albuminuria) in this study, and further investigation is warranted.

Strengths and Limitations

This study has several limitations. Only cases of singleton pregnancies in which renal function tests were performed prior to delivery were included. The maternal renal function tests reviewed in this study were based on blood sample results taken closest to the time of delivery; however, most cases were tested only once, and data over time during pregnancy were not reviewed. Almost all blood tests were performed for maternal screening prior to cesarean section, resulting in earlier weeks in the twin pregnancy group. Cardiac output during pregnancy is reported to vary greatly with maternal posture and uterine size (e.g., amniotic fluid volume); however, there are no quantitative data on these factors. Lastly, we had no data regarding proteinuria (albuminuria) in this study. In future, we would like to examine albuminuria and cystatin C

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levels.

Conclusion

In conclusion, twin pregnancy was found to be a significant risk factor for maternal renal dysfunction (serum creatinine $>$ 0.8 mg/dL). The rate of maternal renal dysfunction was not significantly different between dichorionic and monochorionic twins. In 13 twin pregnancies with renal dysfunction, the renal function of all women normalized after delivery, without medical intervention. This suggests that pregnancy induces maternal renal dysfunction, which is more pronounced in twins. Careful attention should be paid to maternal renal dysfunction in the management of twin pregnancies.

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Disclosure of Interests: The authors declare no conflicts of interest in association with the present study.

Contribution to Authorship: AM was the principal author who participated in the conceptualization, design, data collection and management, and data analysis. HT was the corresponding author, contributed to the design, data collection and management, and data analysis, and drafted the manuscript. YM, TN, MS, NF, YI, AT, TA, and KM contributed to the data collection and management. All authors have read and approved the final manuscript.

Details of Ethics Approval: This study was approved by the Ethics Committee of the Japanese Red Cross Aichi Medical Center Nagoya Daiichi Hospital, Nagoya, Japan (approval date: November 9, 2021; approval number: 2021-422). Informed consent was not required for this study since we used anonymous clinical data.

Data Availability Statement: The data (de-identified participant data) that support the findings of this study are available from the corresponding author (HT) upon reasonable request.

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Table legends

Table 1. Maternal characteristics of this study

Table 2. Maternal renal function during pregnancy between singleton and twin pregnancies

Table 3. Multivariate logistic regression analysis for renal dysfunction (serum creatinine $>$ 0.8 mg/dL)

Table 4. Renal function during pregnancy between dichorionic and monochorionic twin pregnancies

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