

Volume 2 Issue 10 October 2021

# A Case Report of Chronic Kidney Disease and Chronic Hypertension Complicated with Preeclampsia during Pregnancy

# Jianzhen Zhang and Yan Wu\*

Department of Obstetrics and Gynecology, Women and Children's Hospital of Jiaxing University, Jiaxing City, Zhejiang Province, China

\*Corresponding Author: Yan Wu, Department of Obstetrics and Gynecology, Women and Children's Hospital of Jiaxing University, Jiaxing City, Zhejiang Province, China. Received: August 28, 2021 Published: October 14, 2021 © All rights are reserved by Jianzhen Zhang and Yan Wu.

# Abstract

**Rationale:** With the development of the world medical level, most women with chronic kidney disease can successfully conceive under the joint guidance and management of multidisciplinary cooperation. Patients with chronic kidney disease need to be vigilant about hypertension and preeclampsia during pregnancy. Doctors should reduce the risk and complications of pregnancy in women with chronic kidney disease and increase the fetus's survival rate. Enhance collaboration and joint management of such patients through clinical departments.

**Patient Concern:** This article reports on the treatment and pre-and post-natal management of a pregnant woman with chronic kidney disease, chronic hypertension, and preeclampsia. The patient had CKD before pregnancy and was diagnosed with chronic hypertension and type II diabetes during CKD stage 2 during pregnancy.

**Diagnosis:** CKD stage 2, PGDM (type II diabetes), chronic hypertension complicated with preeclampsia, hypertensive retinopathy, one pregnancy, 0 births, 19 weeks and one day of pregnancy.

**Interventions:** The Women's Health Department included this patient in treating high-risk pregnant women and parturients, fulltime staff, dynamic monitoring, and overall management. In this case, the patient is managed through multidisciplinary cooperation, and low-dose aspirin is used to prevent preeclampsia, reasonably lower blood pressure, and control blood sugar.

Outcomes: Although preeclampsia occurred later, the prognosis of mother and child was relatively good.

**Conclusion:** Pregnant women with CKD and preeclampsia and their offspring have an increased risk of ESRD and chronic diseases. The Ministry of Women's Health and the Ministry of Child Health need to cooperate for follow-up observation and timely intervention. The number of pregnant women with CKD is increasing year by year, and these patients are high-risk groups of preeclampsia during pregnancy. Preeclampsia during pregnancy severely affects the pregnancy outcome of patients with CKD and significantly promotes the progress of basic CKD. In clinical work, attention should be paid to the management of such patients during pregnancy. Multidisciplinary cooperation should be used to prevent and treat preeclampsia based on early prevention, close monitoring, and early diagnosis of CKD to improve mothers and children's prognosis.

Keywords: Pregnant Woman; Chronic Kidney Disease; Chronic Hypertension Complicated with Preeclampsia

**Citation:** Jianzhen Zhang and Yan Wu. "A Case Report of Chronic Kidney Disease and Chronic Hypertension Complicated with Preeclampsia during Pregnancy". *Acta Scientific Medical Sciences* 5.11 (2021): 32-38.

### Abbreviations

CKD: Chronic Kidney Disease; ESRD: End-Stage Renal Disease; PGDM: Pre-Pregnancy Diabetes; GLU: Glucose; CREA: Creatinine; UREA: Blood Urea Nitrogen; UA: Uric Acid; BNP: Brain Natriuretic Peptide; PRO: Urine Routine; eGFR: Estimated Glomerular Filtration Rate; PROU: Urine Protein Quantification; HBA1C: Hemoglobin A1C; MDRD: Modified Kidney Disease Diet Formula; MDT: Multidisciplinary Consultation; S/D: Umbilical Artery Blood Flow Ratio; LOA: Left Anterior Occipital Position; NICU: Neonatal Intensive Care Unit; NCPAP: Nasal Continuous Positive Airway Pressure; ASQ-C: Age and Developmental Progress Questionnaire; KDIGO: Kidney Disease: Improving Global Outcomes; NICE: National Institute of Clinical Excellence; The DOHaD Hypothesis: The Developmental Origins of Health and Disease Hypothesis

### Introduction

Pregnancy impacts the renal function of patients with chronic kidney disease (CKD). Pregnancy can cause renal hyperfiltration, increased urine protein, preeclampsia, hypercoagulable state, etc. induce the recurrence or aggravation of the original kidney disease, and endanger the pregnant woman. On the other hand, the original kidney disease makes the kidney function unable to meet pregnancy needs, such as low levels of kidney secretion hormones often lead to anemia and vitamin D deficiency, leading to adverse pregnancy outcomes for pregnant women [1]. Some studies have shown that for patients with CKD 1 to 2 when blood pressure is well controlled and urine protein is maintained < 1 g/24h, pregnancy has little effect on renal function, and the probability of fetal survival is > 95%. For patients in CKD 3 to 5 stages, pregnancy may cause the original CKD to relapse (especially in patients with lupus nephritis) or aggravate, cause irreversible damage to renal function, thereby increasing the risk of end-stage renal disease (ESRD) [1,2]. It can even lead to adverse outcomes such as malignant hypertension, placental abruption, premature birth, preeclampsia, death of pregnant women and fetal growth restriction, and intrauterine death [1]. CKD patients with pregnancy have complex pathophysiological changes and unique treatments. A successful pregnancy requires multidisciplinary cooperation. Carry out a comprehensive plan in various disciplines, including nephrology, obstetrics and gynecology, obstetrics and gynecology, neonatology, rheumatology, and immunology, to complete the treatment pregnant women and newborns. During pregnancy, drug treatment needs to consider the pharmacokinetics changes caused by impaired renal function and the teratogenic effects of the drug on the fetus, and finally select the appropriate drug.

# Case Report Presenting concerns

Pregnant woman, female, Chinese Han people, Electrical company employee, 33 years old, 0-0-0-0, last menstrual period: March/5/ 2019. A history of chronic hypertension and type II diabetes for more than five years, nifedipine controlled-release tablets 10mg, orally, two times a day + metformin tablets 0.5g, three times a day. Her blood pressure monitoring was normal, but her blood sugar was high, her fasting blood sugar fluctuated between 7 - 9 mmol/L, and her blood glucose was not measured after meals. The patient had been infertile for many years. This time it was an unexpected pregnancy, and no evaluation was performed before pregnancy. Self-test urine pregnancy test was positive after 40+ days of menopause. The ultrasound indicated: intrauterine pregnancy, which was consistent with gestational week. The patient immediately stopped nifedipine sustained-release tablets and metformin tablets, and her blood pressure fluctuated around 150/100 mmHg without monitoring her blood glucose. After 61 days of menopause (May/06), the patient felt a headache, no dizziness, ignorance of blurred vision, no chest tightness, no shortness of breath, and self-tested blood pressure 180/110 mmHg. She went to the emergency department of the obstetrics and gynecology department of our hospital immediately. Her blood pressure was measured at 189/110 mmHg. After taking 10mg nifedipine tablets sublingually, her blood pressure gradually dropped to 136/78 mmHg, peripheral blood glucose 10.4 mmol/L, biochemical analysis: GLU 11.28 mmol/L, CREA 88 µmol/L, UREA 5.04 mmol/L, UA 402 µmol/L, BNP 108 pg/ml, urine routine: PRO 3+. The doctor recommended hospitalization, but she refused and left the hospital by herself. The emergency doctor submits a report on the pregnancy risk assessment classification for pregnant women, the pregnancy risk classification is red (high risk), and it is reported to the Women's Health Department of the hospital within 24 hours. The Department of Women's Health is included in the project management of high-risk pregnant and lying-in women according to regulations, establishes a special account, and contacts the grass-roots women's health personnel in the place where the patient's household registration is located to track and urge the patient to see a doctor. The next day

**Citation:** Jianzhen Zhang and Yan Wu. "A Case Report of Chronic Kidney Disease and Chronic Hypertension Complicated with Preeclampsia during Pregnancy". *Acta Scientific Medical Sciences* 5.11 (2021): 32-38.

the patient went to the high-risk obstetric department to check glycosylated hemoglobin determination: HBA1C9.4%, urine sensitive renal function 7 items: urine microalbumin > 1650.00 mg/L, urine transferrin > 120.0 mg/L, urine immunoglobulin IgG 281.4 mg/L, urine N-acyl-β-D-glucosaminidase 17.7U/L, urine retinol-binding protein 8.13 mg/L, urine creatinine 6182.00 μmol/L, urine β2 microglobulin 2.47mg/L; Urine protein quantification: PROU 8347.5 mg/day. Fundus examination: the fundus of hypertension changed in stage II, and there was no noticeable change in the fundus of diabetes (Figure 1). Internal and surgical color Doppler ultrasound: no space-occupying in both kidneys and no stenosis in both renal arteries. Adult cardiac color Doppler ultrasound: the left ventricle is slightly enlarged, the valves are not abnormal, and the left ventricular diastolic function is decreased. Ambulatory blood pressure: 24h blood pressure increased, circadian rhythm inverted, blood pressure increased in the morning. Calculate the estimated glomerular filtration rate (eGFR) according to age and body mass with the modified kidney disease diet formula (MDRD) [3] 74.2 ml/min.1.73 m<sup>2</sup>, diagnosis chronic kidney disease (Chronic Kidney Disease, CKD) stage 2, combined with chronic hypertension, type II diabetes. Blood pressure and blood sugar control are not acceptable. It is recommended to terminate the pregnancy. The patient is eager to give birth, refuses to terminate the pregnancy.



**Figure 1:** The patient's early pregnancy (menopause 62 days) fundus examination + optical coherence tomography (OCT).

### **Clinical findings**

The Department of Women's Health organizes obstetrics, prenatal genetic counseling, nephrology, endocrinology, and neonatology to conduct MDT consultations. The multidisciplinary consultation recommended a treatment plan as follows: Aspirin 100mg, once a day to prevent preeclampsia, 150 mg of Labetalol hydrochloride tablets, orally, once every 8 hours + Nifedipine controlled-release tablets 10mg, orally, twice a day for antihypertensive treatment, and her blood pressure fluctuates around 130/80 mmHg. Insulin as part combined with insulin detemir was injected subcutaneously to lower blood sugar, and the amount of insulin was adjusted according to blood sugar. Control the blood glucose before three meals, fasting and night blood glucose <6.0 mmol/L, and blood glucose within 2 hours after meal < 7.5 mmol/L.

About 27 weeks after menopause, the patient gradually began to feel blurred vision with no headache and no dizziness, and increased blood pressure (up to 160/86 mmHg). Considering complicated preeclampsia, adjust 150 mg of labetalol hydrochloride tablets orally, yonce every 8 hours + 30 mg nifedipine controlledrelease tablets, once a day for active antihypertensive treatment. Monitor urine protein for a continuous 3+, quantitative urine protein fluctuates between 4737.3 - 8347.5 mg/day, renal function: CREA fluctuates at 82-117 umol/L, urine ß2 microglobulin fluctuates at 3.14-3.23 mg/L. High-throughput gene sequencing inspections are low risk. There were no abnormal findings on ultrasound and echocardiography of the fetal system. Obstetric ultrasound fetus size is consistent with gestational age. The Department of Women's Health maintains patient information dynamically and manages it together.

At 29 weeks of gestation, she was admitted to the obstetrics department for a comprehensive assessment of her condition. At the same time, compound betamethasone 12mg was injected intramuscularly, once a day to promote fetal lung maturity, two times in total. During medication, adjust the amount of insulin according to blood sugar. (September 27) Fundus examination results: 1. Hypertensive fundus changes in stage III, 2. Diabetic retinopathy proliferation stage (Figure 2).

The patient with menopause at 33 weeks (October/24) came to the hospital for routine obstetrics, fetal heart rate monitoring nonresponsive type, irregular contractions, S/D 3.133, the conscious fetal movement was expected, and admitted to the maternity ward in the emergency department. Physical examination: T: 36.5°C, P: 86 beats/min, R: 19 beats/min, BP: 150/83 mmHg, clear, mentally stressed, cardiorespiratory, edema 2+, uterine height 31 cm, abdominal circumference 110cm, head, fetal position LOA, fetal heart

**Citation:** Jianzhen Zhang and Yan Wu. "A Case Report of Chronic Kidney Disease and Chronic Hypertension Complicated with Preeclampsia during Pregnancy". *Acta Scientific Medical Sciences* 5.11 (2021): 32-38.



Figure 2: The patient's late pregnancy (menopause 29 weeks + 1 day) fundus examination + optical coherence tomography (OCT).

rate 140 beats/min, occasional contractions, vaginal examination failed, and fetal membranes not broken. After admission, a review of the non-responding type of fetal heart monitoring, an emergency cesarean section was decided. The emergency department prepared for the operation under combined spinal-epidural anesthesia. The neonatologist arrived, and the pregnant woman gave birth to a live baby girl with an Apgar score of 8-8-8, a weight of 2000g, entering the NICU, smooth operation, and intraoperative blood pressure 156 - 120 /110-80 mmHg. After a cesarean section, the recovery is good, blood pressure and blood sugar are controlled smoothly, and urine protein gradually decreases. Urinary protein quantitative 3991.0mg/day, renal function: CREA 115µmol/L, adult cardiac color Doppler ultrasound: left atrium and left ventricle slightly enlarged. Ventricular septum slightly thickened. Each valve is not See abnormal, left ventricular diastolic function decreased.

### **Diagnostic focus and assessment**

Diagnosis: CKD stage 2, PGDM (type II diabetes), Chronic hypertension complicated with Preeclampsia, Hypertensive retinopathy, one pregnancy, one birth, 33 weeks +0 day of gestation, Delivery by emergency cesarean section, Premature delivery. The patient's blood pressure and blood glucose control during the early and second trimester is not ideal, and postpartum follow-up is required.

# Follow-up and outcomes

The patient was discharged from the hospital five days after surgery. The newborn was admitted to NICU to diagnose neonatal respiratory distress syndrome, NCPAP was used to assist ventilation, porcine lung phospholipid was instilled into the trachea, and the recovery was good. Heart color Doppler ultrasound indicated: atrial septal defect (II) and was discharged 21 days after birth. Weight 2525g, head circumference 31.5 cm, body length 46 cm, corrected gestational age 36 weeks + 2 days. The project management of the Women's Health Department tracks patients to 42 days postpartum. The patient's blood pressure and blood sugar tended to be stable in the first month after delivery. (December 11) the 3<sup>rd</sup> time fundus examination: 1. Hypertensive fundus changes in stage II, 2. Diabetic retinopathy (Figure 3), which improved compared to prenatal. The patient was followed up by telephone. At present, the patient takes orally 30 mg nifedipine controlled-release tablets orally, once a day, self-monitored blood pressure fluctuates between 130 - 145/85-98 mmHg, 0.5g metformin tablets, orally, three times a day, self-monitored Fasting blood glucose fluctuates between 7 -7.5 mmol/L. Follow-up glomerular filtration rate (eGFR) fluctuated between 72.1 - 101.2 ml/min.1.73m<sup>2</sup>, which was CKD1 stage. The Department of Neonatal and Child Health is included in the followup management of high-risk infants and follow-up in every two months for a year after birth. The child care examination's body mass and height were all up to the standard, and the scores of the Chinese version of the Age and Developmental Progress Questionnaire (ASQ-C) were average.



**Figure 3:** The patient's postpartum (40 days postpartum) fundus examination + optical coherence tomography (OCT).

# **Discussion and Conclusion**

CKD is complicated with pregnancy, the onset is insidious and slow, and renal dysfunction during non-pregnancy may not sig-

**Citation:** Jianzhen Zhang and Yan Wu. "A Case Report of Chronic Kidney Disease and Chronic Hypertension Complicated with Preeclampsia during Pregnancy". *Acta Scientific Medical Sciences* 5.11 (2021): 32-38.

nificantly impact. As the pregnancy progresses, the kidney load increases and the renal dysfunction worsens, which seriously endangers mothers' and children's lives [4,5]. The risk of preeclampsia in pregnant women with CKD is significantly increased. The severity of CKD, whether chronic hypertension, diabetes, and kidney disease etiology, is closely related to preeclampsia risk during pregnancy. The concurrent preeclampsia based on CKD will seriously affect newborns' prognosis and accelerate maternal primary kidney disease [6]. For patients with CKD and chronic hypertension, a joint consultation of obstetrics, cardiology, nephrology, rheumatology, immunology, and neonatology should be conducted to evaluate the patient's condition and formulate a proper monitoring and treatment plan, coordinate and cooperate, and jointly manage this category Patient [7].

Many patients with basic CKD also have chronic hypertension [8]. Both CKD and chronic hypertension are high-risk factors for preeclampsia during pregnancy. The blood pressure control of such patients plays a vital role in preventing preeclampsia occurrence during pregnancy. The clinical guidelines for hypertension in pregnancy generally believe that the blood pressure control level of patients with chronic hypertension in pregnancy does not need to be as strict as that of non-pregnant people, but patients with organ damage should be strictly controlled. For patients with CKD, it should be regarded as organ damage. Therefore, the blood pressure control standards for such patients during pregnancy should be more stringent. Both KDIGO and NICE recommend that CKD patients' blood pressure without proteinuria should be controlled at < 140/90 mmHg, while those with urine protein or diabetes should be controlled at < 130/80 mmHg [9,10]. A large number of studies have confirmed that low-dose aspirin has a specific preventive effect on the occurrence of preeclampsia in patients with high-risk factors. The USPSTF's definition of high-risk groups of preeclampsia includes patients with CKD [11]. ACOG also treats patients with CKD as a high-risk group with preeclampsia [12].

If it is accompanied by active nephritis, blood creatinine value > 150 umol/L, endocarditis, myocarditis, progressive glomerulonephritis, nephrotic syndrome, and deterioration of the condition early and middle pregnancy, and intrauterine distress, the pregnancy should be terminated in time. After 36 weeks of pregnancy, a further increase in blood pressure may cause fetal death in utero, deterioration of renal function, and pregnancy termination should also be considered [13]. Preeclampsia during pregnancy in pregnant women with CKD will increase postpartum end-stage renal disease (ESRD) [9,14,15]. The DOHaD hypothesis believes that in addition to genetic and environmental factors, if life experiences unfavorable factors in the early stages of development, it will increase the risk of obesity, diabetes, cardiovascular disease, asthma, tumors, osteoporosis, neuropsychiatric diseases, and other chronic diseases in adulthood probability [10,16]. Therefore, patients with CKD and preeclampsia and their offspring should strengthen postpartum follow-up monitoring and timely intervention.

Considering that the patient had CKD before pregnancy, renal function decreased with the increase of pregnancy and was diagnosed as CKD stage 2 according to MDRD [7,17]. Given the concurrent chronic hypertension and type II diabetes, which are high-risk factors for preeclampsia, the risk of continuing pregnancy is higher for mothers and children [17-20]. However, there is not enough evidence to list CKD as an absolute contraindication for pregnancy [20]. The patient has been infertile for many years after marriage and is eager to give birth and is unwilling to terminate the pregnancy. The Department of Women's Health has incorporated it into the project management of high-risk pregnant and lying-in women for dynamic monitoring and full-process management. Simultaneously, multi-disciplinary cooperation and joint management of patients give small doses of aspirin to prevent preeclampsia, reasonably lower blood pressure and control blood sugar. Although preeclampsia occurs later, the prognosis of mother and child is relatively good. Patients with CKD preeclampsia in pregnant women and their offspring have an increased risk of ESRD and chronic diseases [15,21,22]. The Women's Health Department and Child Health Department must work together to follow-up observation and timely intervention.

#### **Key Clinical Message**

Patients with chronic kidney disease combined with preeclampsia and their offspring are at increased risk of postpartum endstage renal disease (ESRD) and chronic disease, which requires joint collaboration between the women's health and child health departments for follow-up observation and timely intervention.

### **Competing Interests**

The authors declare no potential conflicts of interest with respect to the research, authorship, or publication of this article.

**Citation:** Jianzhen Zhang and Yan Wu. "A Case Report of Chronic Kidney Disease and Chronic Hypertension Complicated with Preeclampsia during Pregnancy". *Acta Scientific Medical Sciences* 5.11 (2021): 32-38.

# **Funding Info**

We received no financial support for the research, authorship, and/or publication of this article.

# **Author Contribution**

All authors participated substantively to the paper and have approved the final version of the manuscript.

# **Conflict of Interest**

The authors declare no potential conflicts of interest with respect to the research, authorship, or publication of this article.

# **Consent to Publish**

None of the content is included in another manuscript, has been published previously, or is currently under consideration for publication elsewhere.

# Statement

The patient has provided informed consent to announce the case.

# **Bibliography**

- 1. Bramham K., *et al.* "Pregnancy Outcome in Women with Chronic Kidney Disease: A Prospective Cohort Study". *Reproductive Sciences* 18.7 (2011): 623-630.
- Andrassy KM. "Comments on 'KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease". *Kidney International* 84.3 (2013): 622-623.
- LAEKe. "Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes". *Kidney International* 67.6 (2005): 2098-2100.
- Zhang JJ., et al. "A Systematic Review and Meta-Analysis of Outcomes of Pregnancy in CKD and CKD Outcomes in Pregnancy". *Clinical journal of the American Society of Nephrology: CJASN* 10.11 (2015): 1964-1978.
- Yuan MX., *et al.* "[Construction and validation of pregnancy risk prediction model for pregnant women with chronic kidney disease]". *Zhonghua fu chan ke za zhi* 55.3 (2020): 172-176.

- Yingdong H. "Chronic kidney disease and preeclampsia". *Chinese Journal of Practical Gynecology and Obstetrics* 05 (2018): 480-484.
- 7. Yan W. "Research progress of pregnancy-related problems in women with chronic kidney disease". *Chinese Journal of Practical Gynecology and Obstetrics* 05 (2018): 480-484.
- 8. Piccoli GB., *et al.* "Risk of Adverse Pregnancy Outcomes in Women with CKD". *Journal of the American Society of Nephrology* 26.8 (2015): 2011-2022.
- Spaan JJ and Brown MA. "Can we protect the kidneys after hypertensive pregnancy?". *Canadian Medical Association Journal* 185.3 (2013): 199-200.
- 10. Redman CW. "Hypertension in pregnancy: the NICE guidelines". *Heart* 97.23 (2011): 1967-1969.
- 11. LeFevre MLJAoim. "Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: US Preventive Services Task Force recommendation statement 161.11 (2014): 819-826.
- ACOG Committee Opinion No. 743: Low-Dose Aspirin Use During Pregnancy". *Obstetrics and Gynecology* 132.1 (2018): e44e52.
- 13. Ying Xing. "Multidisciplinary collaboration in the management of chronic kidney disease complicated with pregnancy". *Clinical Review* 06 (2016): 610-614.
- McDonald SD., et al. "Kidney Disease After Preeclampsia: A Systematic Review and Meta-analysis". American Journal of Kidney Diseases 55.6 (2010): 1026-1039.
- 15. Wang I-K., *et al.* "Association between hypertensive disorders during pregnancy and end-stage renal disease: a population-based study 185.3 (2013): 207-213.
- Young EC., *et al.* "Effects of pregnancy on the onset and progression of diabetic nephropathy and of diabetic nephropathy on pregnancy outcomes". *Diabetes and Metabolic Syndrome* 5.3 (2011): 137-142.
- 17. Xie M., *et al.* "[Analysis of the perinatal outcome and risk factors for pregnancies complicated with chronic renal diseases]". *Zhonghua fu Chan Ke Za Zhi* 47.3 (2012): 161-165.

**Citation:** Jianzhen Zhang and Yan Wu. "A Case Report of Chronic Kidney Disease and Chronic Hypertension Complicated with Preeclampsia during Pregnancy". *Acta Scientific Medical Sciences* 5.11 (2021): 32-38.

- Wiles KS., *et al.* "Reproductive health and pregnancy in women with chronic kidney disease". *Nature Reviews Nephrology* 14.3 (2018): 165-184.
- 19. Wiles KS., *et al.* "Pre-pregnancy counselling for women with chronic kidney disease: a retrospective analysis of nine years' experience". *BMC Nephrology* 16 (2015): 28.
- 20. Wiles K., *et al.* "Updates in Diagnosis and Management of Preeclampsia in Women with CKD". *Clinical Journal of the American Society of Nephrology: CJASN* 15.9 (2020): 1371-1380.
- Wiles K., *et al.* "Diagnostic Indicators of Superimposed Preeclampsia in Women With CKD". *Kidney International Reports* 4.6 (2019): 842-853.
- Vadalà C., et al. "[Long-term outcome of renal function in women with preeclampia and pregestational diabetes]". Giornale Italiano di Nefrologia: Organo Ufficiale Della Societa Italiana di Nefrologia (2017): 34.

# Volume 2 Issue 10 October 2021 © All rights are reserved by Jianzhen Zhang and Yan Wu.