

Werner syndrome associated with renal involvement

*Gonenc Kocabay, MD, Sukru Ozturk, MD,
Tevfik Ecdar, MD.*

Werner's syndrome (WS) is an autosomal recessive disease, which is characterized by premature aging, short stature, cataract, dermal atrophy and ulcers, turning white early on hairs, alopecia, vascular calcification, diabetes mellitus, and osteoporosis.^{1,2} Kidney involvement is rarely seen in WS.^{3,4} We report a case of WS associated with end stage renal failure without any risk factor.

A 29-year-old male patient with no previous complaints, was admitted to our clinic complaining of left lumbar pain, oliguria, and an ulcer on the second finger of the left hand. His parents were not consanguineous, and he had healthy siblings. His physical examination revealed conjunctival pallor, bird-like face, squeaky voice, short stature (150 cms, below 3%), not well-proportioned diffused dermal atrophy for his age, whitening on hair and alopecia, muscular atrophy especially on arms, and dermal changes on hands similar to scleroderma. He had an ulcer on the second finger of his left hand, and other systemic examinations were found normal. His blood pressure was 130/80 mm Hg and pulse rate was rhythmic and 76/minute. His laboratory findings were as follows: hemoglobin 11 gr/dl, hematocrit 33%, mean corpuscular volume 90 fl, leucocyte 6700/ml, neutrophil 4400/ml, lymphocyte 1600/ml, and thrombocyte 160000/ml. The serum biochemical analyses were as follows: glucose 90 mg/dl, blood urea nitrogen 64 mg/dl, creatinine 4.6 mg/dl, uric acid 6.6 mg/dl, sodium 125 mmol/l, potassium 4.8 mg/l, chlorine 80 mmol/l, calcium 8.6 mg/dl, phosphor 3.9 mg/dl, lactate dehydrogenase 335 U/l (normal: <225 U/l), total protein 6.4 gr/dl, albumin 3.4 gr/dl, total cholesterol 140 mg/dl, low density lipoprotein cholesterol 80 mg/dl, triglyceride 107 mg/dl. The serum thyroid stimulating hormone, luteinizing hormone, follicle stimulating hormone, and testosterone levels were found normal. The serum parathormone level was 245 pg/ml (normal:15-65 pg/ml). His urine analysis showed 1(+) proteinuria, and proteinuria was 1.25 gr/day on Esbach test. Urine sodium was found approximately 19 mmol/l. His electrocardiographic

and echocardiographic investigations were normal. Anticardiolipin IgG and IgM antibodies, antinuclear antibody, anti-neutrophil cytoplasmic antibody, and lupus anticoagulant factor analyses were found negatively. Factor V Leiden mutation could not be found. The glomerular filtration rate was calculated as 20 ml/minute by the Cockcroft-Gault formula. Both kidney dimensions were found bilaterally smaller than normal on abdominal ultrasonography. A cataract could not be found on eye examination. Increased fragility could not be found on chromosome analysis. He was diagnosed as "Possible Werner syndrome" by Nakura et al criteria,¹ which was developed for this syndrome. Werner syndrome was diagnosed by 4 major findings, such as, characteristic dermal changes, short stature, turning white early on hair, alopecia, bird-like face, and squeaky voice. For his treatment, renal transplantation was performed.

Werner syndrome is a rarely seen disease, which follows as an autosomal recessive pattern. Premature aging in WS occurs during the pre-adolescent period, and patients are usually lost in 45-50 years of age by causes such as, myocardial infarction, cerebrovascular accidents, and cancer. These are caused by atherosclerosis, which is usually associated with this syndrome. Mutation of the Werner gene may be found by sequence analysis in WS. However, diagnostic genetic test has not been suggested. Increased chromosomal aberrations after exposure to clastogens, which are not diagnostic, may be found. According to physical examination findings, WS is diagnosed by Nakura et al¹ diagnostic criteria, which are classified in 3 categories such as definite, probable, and possible diagnosis. According to criteria of Nakura et al,¹ the present case was in accordance with possible diagnosis of WS.

End stage renal failure is rarely seen in WS.^{3,4} Kawamura et al⁴ reported a case of WS who developed end stage renal failure 17 years later. Hypertensive glomerular nephrosclerosis was found on his renal biopsy. Therefore, hypertension was considered responsible for renal failure. According to the literature review, Haddad et al⁵ reported a case of WS who had renal failure due to urologic disease. Nishihara et al³ reported a case of WS who was diagnosed at 51 years of age and developed diabetes mellitus and nephrotic proteinuria. Diabetes mellitus was not considered as the cause of renal failure by reason of having no diabetic retinopathy, and the finding of bilaterally small kidney dimensions in this patient. Our patient

did not have diabetes mellitus and hypertension. For this reason, the etiology of renal failure might be due to a different cause. Werner syndrome developed renal failure without any risk factor, and raises the question: Is renal involvement a rare seen component of werner syndrome?

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From the Department of Internal Medicine (Kocabay), Department of Medical Genetics (Ozturk), and the Department of Nephrology (Eceder), Istanbul School of Medicine, Istanbul University, Istanbul, Turkey. Address correspondence and reprint requests to: Dr. Gonenc Kocabay, Department of Internal Medicine, Istanbul School of Medicine, Istanbul University, Istanbul, Turkey. Ahmet Vefik Pasa Caddesi Yasam Apartmani, No. 60 Kat 2 Daire 2 Capa/Istanbul, Turkey. Tel. + 90 (532) 5180035. Fax. + 90 (212) 5205858. E-mail: gonenckocabay@yahoo.com/gkocabay@istanbul.edu.tr

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Pregnancy outcomes and complications in advanced maternal age

*Sedigheh Ayaty, MD,
Fatemeh VahidRoudsari, MD,
Mohammad T. Shakeri, PhD,
Zohreh Yousefi, MD.*

During the past decade, the proportion of women giving birth age ≥ 35 has significantly increased. There are numerous complications of pregnancy-affecting both the mother and fetus among these women. Although there is no precise age beyond which a woman becomes more susceptible to those complications, the age of 35 is frequently used as a cut-off, especially in referring to women who are pregnant for the first time.¹ It is well known that older pregnant women are more susceptible to adverse

outcomes of pregnancy for both nulliparous as well as multiparous older women.² Because the incidence of most chronic medial illnesses and surgical complications accrues as a function of age, it is not surprising that these complications are encountered more frequently in older pregnant women. For example chronic hypertension complicated 10-20% of pregnancies in women over 35 instead of 5-6% in age of 20-25. As emphasized by some studies, older women with medical conditions are at greater risk of postpartum complications, especially thrombosis, pulmonary edema and heart failure.² Salihi et al,³ found that the incidence of maternal bleeding from both placental abruption, and previa increased in women >35 . It seems logical that placental abruption for both nulliparous and parous older women is higher due to chronic hypertension. The cesarean birth rate also increased substantially. Others found that the risk of cesarean section doubled in these women that is an independent risk factor, and suggested that physician and patient concern for pregnancy outcome in older women may be etiological.⁴ According to these finding, it is not surprising that maternal mortality rates increased about 4-fold compared to younger women.⁵ With increasing maternal age, fewer pregnancies end in live birth because of concomitant increases in spontaneous abortion, stillbirth, preterm delivery and restricted fetal growth. Older woman have a higher incidence of macrosomic infants, congenital malformations and perinatal mortality. Pregnancy after 35 is increasingly common in our society, and preconceptional counseling improved prenatal and obstetrical care has made advanced maternal age compatible with successful pregnancy for the great majority of such women. Therefore, in the present study, the obstetric outcome in advanced maternal age (>35 years old) and young women (20-30) were compared.

This retrospective cross-sectional case-control study was performed over a period of one year in Qaem and Hazrat-e Zeynab Hospital, affiliated to Mashhad University of Medical Sciences, Mashhad, Iran. One hundred and seventy pregnant women aged ≥ 35 with a mean age of 37 ± 2.9 years (case group) and 170 women aged 20-30 years with a mean age 25.3 ± 3.1 years (control group) were matched. The personal and medical information and pregnancy outcome was filled out in a questionnaire for all patients. Past obstetrical information such as the number of abortions, pregnancies, deliveries, alive neonate, fetal deaths, and present pregnancy information, past and maternal and neonatal outcome were reviewed. The method of delivery was evaluated in both groups.

Statistical analyses were performed by SPSS version 11.5 software. We used t-student, Mann Whitney and Chi-square tests. The Multiple Logistic Regression Analysis was used for calculating the point and interval estimation of odds ratio regarding dependent variables. A probability value of ± 0.05 were considered statistically significant. The results showed that frequency of poor pregnancy outcome and complications were higher in the case group than control group. These differences were statistically significant in cesarean section rate, abortion prevalence, third trimester bleeding, need to transfusion, post partum problems such as manual revision of placenta and medical problems such as hypertension, diabetes mellitus and anemia (hematocrit $< 30\%$). The prevalence of neonatal complications in the study group were more than the control group such as: 1) preterm labor (19.7% versus 9.9%, $p=0.05$). 2) One-minute apgar scores of ≤ 3 (7.7% versus 1.2%, $p=0.01$). 3) Macrosomy, birth weight > 4000 gram (12% versus 4%, $p=0.03$). 4) Still birth (4.1% versus 0.6%). Also, the prevalence of thin meconium, asphyxia, respiratory distress syndrome (RDS), anomalies and neonatal death were higher than control group. We used regression analysis to determine the effect of maternal age on pregnancy complications, and found that maternal age was an independent risk factor in pregnancy; especially the prevalence of medical problems (hypertension and diabetes mellitus during pregnancy) and some obstetrical complications such as abortion will be increased by advanced maternal age. We found that maternal age was not an independent risk factor in neonatal problem; it means that mothers with advanced ages probably have the same neonatal outcome. For women in good health who receive appropriate prenatal care, maternal outcome may be expected to be good, even for women over the age of 45.² Approximately 10% of pregnancies occur in women in ≥ 35 years. Our study showed no statistically significant difference between the 2 groups with respect to medical disorders such as urinary tract infection, gestational diabetes but there was a significant difference in hypertension and anemia between 2 groups. There were significant differences in cesarean section rate, abortion and third trimester bleeding between the 2 groups. There were more perinatal death and preterm delivery and one-minute apgar score of < 3 in older women. The results were supported by similar previous studies.²⁻⁴ Some studies indicated that women are at increased risk for maternal and perinatal complications due to the underlying chronic disorders, and our study confirms this information. Therefore, older women who have chronic illness or who were in poor physical

conditions have more risk than physically fit women without medical problems. In our study, we found that the risk of pregnancy medical complications were 5 times more than the control group. Maternal mortality is higher in these women, but improved medical care may ameliorate this risk. Maternal age-related fetal risk primarily stem from: 1) iatrogenic preterm delivery due to medical condition. 2) spontaneous preterm delivery. 3) fetal growth disorders related to chronic maternal disease or multiple gestation. 4) fetal aneuploidy. 5) pregnancies resulting from use of assisted reproductive technology (ART).

In our study, preterm delivery, one-minute apgar score of < 3 and macrosomia was significantly higher in the study group, but the maternal age was not an independent effective factor on neonatal problems. The prevalence of congenital anomalies was higher in the study group but it did not have any statistically significant difference. Other studies confirmed this result as well.^{2,4} We found that maternal age is a risk factor for poor pregnancy outcome, especially its medical conditions, but unless any other disease exist, the neonatal outcome is desirable. So, according to this study the maternal age should not be the only indication of cesarean delivery for improving fetal outcome. Women should realistically appraise the risks of pregnancy after 35 that is increasingly common in our society but improved obstetrical care has made advanced maternal age compatible with successful pregnancy for the great majority of such women.

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From the Department of Obstetrics and Gynecology, Mashhad University of Medical Sciences, Mashhad, Iran. Address correspondence and reprint requests to: Dr. Seddigheh Ayaty, Assistant Professor, Department of Obstetrics and Gynecology, Ghaem Hospital, Mashhad, Iran. Tel. +98 (511) 8417493. Fax. +98 (511) 8409612. E-mail: ff_yahid@yahoo.com

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