



Exceptional Fertility and Poor Fetal Outcome in a Female with 17-Year Hemodialysis: A Case Study and Mini-review

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Authors' contributions

Author AFM gave the research idea and designed the study. Author AZAGA did the data acquisition. Author EHH did the data analysis/interpretation. Author NSA supervised or mentorship the study. Author AFM took the responsibility that this study has been reported honestly, accurately and transparently and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Case Study

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ABSTRACT

Background: Chronic kidney disease can affect different aspects of female patient's life including menstrual pattern, marital status and sexuality, fertility, pregnancy outcome, and recommended methods of contraception especially when initiated on HD.

In Egypt, it has been noticed that it is infrequent for a hemodialysis (HD) female to start her marriage after initiation of HD; this may be attributed to a negative self-image experienced by the patient and perceived by the community. Moreover, it is also less common for an HD patient to marry another HD partner and it is odd for them to conceive during HD.

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Aim: To describe the possibility of starting family and plan for successful pregnancy during the course of HD therapy in patients with ESRD.

Patient Scenario: Our case is a 36 years old Egyptian female who started HD in 1999 and continued on HD for 17 years. She married four times and conceived five times from three husbands. She got live birth only once from her second HD husband, but unfortunately, the baby died within a few days. The patient used Implanon - with its possible side effects- as a method of contraception during her last four years of life. After hectic 17 years under HD and unfortunate marital and fertility events, she decided to withdraw from her dialysis program, chose to live in isolation, and passed away within five days as a consequence of cerebral hemorrhage.

Results and Conclusions: Fertility and successful pregnancies are believed to be possible in HD couples if they receive proper care.

Keywords: Contraceptive method; Egypt; fertility; hemodialysis; pregnancy.

ABBREVIATIONS

<i>Hemodialysis</i>	<i>HD</i>	<i>end stage renal disease</i>	<i>ESRD</i>
<i>Hepatitis B virus</i>	<i>HBV</i>	<i>Hepatitis C virus</i>	<i>HCV</i>
<i>Human immunodeficiency virus</i>	<i>HIV</i>	<i>urea reduction ratio</i>	<i>URR</i>
<i>Erythropoietin</i>	<i>EPO</i>	<i>Intravenous</i>	<i>IV</i>
<i>luteinizing hormone</i>	<i>LH</i>	<i>intrauterine device</i>	<i>IUD</i>
<i>chronic kidney disease mineral bone disease</i>	<i>CKD.MBD</i>	<i>Chronic kidney disease</i>	<i>CKD</i>
<i>Anti-mullarian hormone</i>	<i>AMH</i>	<i>antral follicle count</i>	<i>AFC</i>

1. INTRODUCTION

Patients with end-stage renal disease (ESRD) treated by regular HD are infrequent to start successful marital relationship and to successfully conceive and give birth to live newborn, a limitation in normal life activity that might lead to frustration or mood depression of these patients. It would be interesting to document cases with persevered desire and ability to overcome such limitation.

When patients develop chronic kidney disease (CKD), every organ function of the body is affected, including sexual function [1]. It is now well-established that both men and women with CKD have significant fertility and hormonal deficits associated with uremia. It is an underestimated problem in both genders and has not been evaluated comprehensively. The degree of fertility impairment seems to be related to the stage of CKD, which is most evident in ESRD, and this impairment is explained by some observations. The imbalance in gonadotropin production in dialysis-dependent men and women is characterized by elevations in luteinizing hormone (LH) [2,3]. In female dialysis patients, the normal estradiol-stimulated LH surge does not occur, resulting in anovulation. In male dialysis patients, spermatogenesis is

impaired and low testosterone levels cause elevated LH. High frequency of infertility in those with ESRD may be attributed to impotence (in males), decreased libido, anovulation (in females), and an altered hormonal milieu. Despite these inhibitors of conception, women on dialysis can conceive. Male subfertility or infertility could also be due to hypogonadism, and direct impairment of spermatogenesis with spermatotoxicity and late-stage maturational arrest causing oligospermia or azoospermia. Impaired gonadal function is prominent in uremic men, whereas the disturbances in the hypothalamic-pituitary axis are subtler [4].

Similarly, the probability of achieving pregnancy is significantly lower in women on HD than in the general population, with some studies reporting a pregnancy rate of only 1-7% in this group of patients [5]. Women with CKD are known to have many endocrinal disturbances which lead to ovarian dysfunction and reduction in their fertility. HD patients usually experience fatigue and psychosocial factors related to the presence of chronic disease states that represent contributing factors in impairing fertility. Furthermore, women receiving HD frequently have premature menopause [6]. Therapy is initially directed toward optimizing the dialysis dose, correcting anemia with recombinant erythropoietin, and

management of chronic kidney disease mineral bone disease (CKD-MBD). Kidney transplantation remains the gold standard for improving both the quality and quantity of life, particularly in young adults; including restoration normal sexual function in both men and women with CKD [7].

Multiple research engines in medicine (PubMed –Medscape- Google scholar-science direct, etc.) were screened to find out publications about fertility in HD patients in Egypt and were subsequently examined and analyzed to prepare this minireview.

A few numbers of studies dealing mainly with sexual function and fertility in CKD patients on renal replacement therapy in Egypt were found. During our search, we encountered only four studies evaluating fertility in HD patients in Egypt (two in males and two in females) and four studies evaluating sexual functions in both sexes after renal transplantation (three in males and one in females).

The first of all studies was published in 1992 by Sobh et al. at Mansoura Urology and Nephrology center, Egypt, that discussed the effect of erythropoietin on sexual potency in six male dialysis patients. They were subjected to Doppler study of the deep penile arteries and intracavernosal injection of 30 mg papaverine under basal conditions before and after erythropoietin therapy. The latter authors concluded that erythropoietin treatment could improve sexual potency in uremic patients [8].

Another study was done in upper Egypt titled "Erectile dysfunction in chronic renal failure patients undergoing HD in Egypt" by Ali et al. (2005) explored 75 HD male patients aged between 20 and 69 yrs, with CKD undergoing HD at Assiut University Hospitals. The authors suggested that a complete health evaluation of male HD patients should include a discussion about erectile function in the standard clinical care program of patients with renal disease [9].

A study carried out in Egypt in 2015 by Aldeeb et al. was designed for the evaluation of gynecological problems among Egyptian HD women. The authors observed for six months 62 patients who had been on HD for at least three months, with ages ranging from 18 to 45 years. This study was conducted at the HD unit in El-Mahalla general hospital applying a

questionnaire form, which included the assessment sheet and menstrual cycle questionnaire [10]. The Results of the current study revealed that menstrual disorders, menometrorrhagia, intermenstrual bleeding, oligomenorrhea, and secondary amenorrhea were highly significant prevalent among HD women. More than two-fifths of these women had abnormal vaginal discharges, and near one-third of them had galactorrhea. The authors recommend the application of continuous monitoring for any menstrual or gynecological abnormalities occurring during HD and referral for the gynecological clinic.

Another study by Fayed et al. [11] was carried out on sixty women with ESRD treated by regular HD; 20 of them were planned to have a renal transplant. The authors of this study concluded that HD women with CKD have significantly lower anti-Mullerian hormone (AMH) levels and total antral follicle count (AFC) than age-matched healthy controls. Moreover, a significant reduction of serum AMH and AFC was found after successful renal transplantation, which indicates a reduction of ovarian reserve in patients with CKD that even decline after kidney transplantation. Cryopreservation for the ova could be considered for those patients in future studies, and this technique may be used to preserve their fertility potentiality.

In Egypt, the fertility of both genders in HD patients has not been well investigated so far. Moreover, Egyptian fertility studies on HD females were even much less frequent compared to similar studies in corresponding males. Few published studies had the main focus on the fertility of patients following successful kidney transplantation. Retrospective multicenter observational study on pregnancy in Egyptian HD females, carried out by our team, was accepted as a poster presentation in International Society of Nephrology (WCN, 2020) [12].

2. PRESENTATION OF THE CASE

This case has been the first to be encountered in our experience in HD units, in which a male and a female, both on long-standing HD, were engaged in a marital relationship and gave a live-born neonate.

A 36-years-old Egyptian female started HD at the age of 19 during 1999, after a history of congenital urinary bladder dysplasia and chronic

pyelonephritis. At the initiation of dialysis, she used to pass a reasonable amount of urine. The patient had associated hypertension, and she was initially negative for hepatitis B, hepatitis C, and human immunodeficiency viral infection (HBV, HCV, and HIV) based on serological tests. Chest, heart, and abdomen were clinically free, and there were no abnormalities detected in abdominal ultrasound. There was the only history of infrequent chest infections. Blood pressure was in reasonable control with Amlodipine, Bisoprolol, and Enalapril. There was continuous monthly follow up investigations and management. Hemoglobin level was maintained between 11-13 gm/dl.

She continued regular HD for 17 years. Her HD details included 4-hour sessions three times/week, relying on bicarbonate-based dialysate, with a blood flow rate of 300 ml/min and a dialysate flow rate of 500 ml/min, utilizing a functioning left brachiocephalic fistula, maintaining a range of urea reduction ratio (URR) from 60 – 70%. She was satisfactorily compliant with her regular follow-ups and prescribed medications. After a hectic but optimistic 17-year history on HD with dramatic marital and fertility events, she decided to withdraw from her dialysis program, chose to live in isolation, and passed away within five days as a consequence of massive cerebral hemorrhage after her last HD session.

Regarding her menstrual history, menarche was at 15 years, and menstruations had been regular lasting for five days before starting her HD; however, it began to be irregular after HD. In the last four years of her life, she developed menorrhagia, probably related to contraception with a sub-dermal implant of Implanon (which continued for four years till her death). The patient was 5th gravida, primipara, and aborted four times. She was married four times – all while on HD: The 1st marriage lasted for around two years, followed by a divorce, and she got pregnant twice. Unfortunately, she had first-trimester abortions in both pregnancies. After two years of living single, the patient was subsequently married again to an HD patient who was 50 years old hypertensive and HCV hepatic patient and was dialyzed in the same unit. This time the patient got pregnant again with preterm labor of a female baby at 30 weeks. Unfortunately, the baby died following her admission to the neonatal department for a few

days. Again, this second marriage lasted for only two years and ended with the death of the husband, suffering from deterioration of his chronic liver disease.

After five years of being a widow, the patient was married again. This third marriage yielded two pregnancies, but she was aborted in both after around 16 weeks of pregnancy. Hence, the patient and her family decided to abandon the idea of getting pregnant anymore to avoid daily dialysis during pregnancy, and therefore subdermal etonorgestril (Implanon) was prescribed. The cause of recurrent abortions was not assessed by gynecologists, but it was assumed by the treating nephrology team to be as a result of uremia.

In 2014 the patient suffered from hip dislocation that was not preceded by significant trauma and had menorrhagia; both could possibly be side effects to Implanon. She was then subjected to hip replacement, which was complicated by blood loss necessitating multiple transfusions followed by the development of HCV seroconversion. In spite of the operation, she remained bound to her wheelchair. She subsequently developed progressive depression that necessitated multiple psychiatric consultations with the use of different anti-depressive drugs. This depression was aggravated further when she was transferred to another dialysis room, leaving her old intimate colleagues. One year later, she put an end to her third marriage after four years. She got a 4th unsuccessful marriage, which lasted only for a few months. Consequently, her depression reached its peak, and she started to express her desire to withdraw from HD. Amazingly, the intradermal contraceptive remained in place and was probably forgotten for her remaining year till her death.

During each pregnancy, the patient was subjected to intensified HD; 16 hours/week in the first trimester and 24 hours/week in second and third trimesters. The dry body weight was adjusted weekly with an increment of 0.5 kg/week, and hemoglobin level was maintained above 10 g/dl through adequate doses of subcutaneous erythropoietin (EPO) and intravenous (IV) iron. Hypertension was controlled by Aldomet. The patient was placed on an unrestricted diet. The last three sets of her routine lab analysis are shown in Table 1.

Table 1. Set of three-month routine investigation

	Hemoglobin	Serum. Creatinin pre-dialysis	Blood Urea pre-dialysis	Blood Urea after dialysis	Parathyroid hormone level,	Serum. calcium	Serum. phosphorus
September 2016	13.2	7.9	132	50			
October 2016	13.	7.9	138	52			
November 2016	13.3	8.6	137	55	137.8	8.4	2.4

3. DISCUSSION

It seems interesting to present fertility in a married couple, both are HD patients and to discuss the possible complications of a particular hormonal method of contraception during HD.

Our current HD female patient was young and had residual kidney function at the start of HD and had regular menstruation before the start of HD. The patient received regular EPO during the whole course of HD (32000 IU/month) associated with efficient HD, proper nutrition, and hemoglobin level above 11 g/dl. Our patient was able to conceive at many different and difficult situations but only reached premature delivery with daily HD sessions and physical and psychological support of her second husband (HD patient) and HD staff, but unfortunately, the baby died four days after delivery.

Schmidt et al. [3] discussed the possibility of fertility in both males and females on HD. The influence of dialysis mode, recombinant human EPO, and dialysis adequacy on conception among patients of either sex on dialysis is unknown. Piccoli et al. [13] suggested that having a baby while on dialysis is not impossible, though early neonatal mortality remains high. Pregnancy on HD can occur more often than previously thought [14].

In our case, trials to complete frequent pregnancies by daily dialysis and its failure forced the patient to use Implanon. Implanon (etonogestrel) is released into the circulation and is approximately 100% bioavailable and is metabolized in liver microsomes by the cytochrome p450 3A4 isoenzyme. The biological activity of etonogestrel metabolites is unknown. Excretion of etonogestrel is mainly in urine and to a lesser extent, in feces, and there are no formal studies conducted to evaluate the effect of renal disease on the pharmacokinetics of Implanon [15]. Injudicious use of Implanon was experienced in our patient as she was not informed by the possible side effects and the need to remove Implanon if certain adverse effects occurred; consequently, it was forgotten entirely even after the development of its potential complications. Yildizbas et al. [16], found that 58.5% of women used Implanon in his study removed it because of abnormal bleeding, mood changes appeared in 17.1% of his studied group, and only females complained of depressive symptoms requiring treatment. Additionally, Gezginc et al. [17] concluded that

patients considering the use of Implanon must be carefully selected and informed about its expected side effects before placement. The depressive mood disorder is one of the recorded side effects in their study. Women using Implanon and with a history of depression should be carefully observed. Implanon should be removed if depression, emotional lability and hypertension are aggravated [15].

Pongsatha et al. [18] stated that the long-term use of Implanon seemed to have a negative impact on the mineral density of the distal radius and ulna. This similarity may partially explain the hip dislocation that was experienced by our patient. However, further investigations were not done to exclude other possible causes.

Holley et al. [2] stated that discussions between the women and their nephrologists about possible pregnancy and contraception were reported by only 13% of women. This is in concordance to the situation of our patient as she was not informed by the possible side effects of different contraceptive methods.

Aldeeb et al. [10] and Deniz et al. 2011 found that only less than half of women on HD were using contraceptive methods, mostly intrauterine devices (IUD), contraceptive pills, one-month injection, and tubal ligation. There is a rarity of published data in finding the most proper contraception method in HD women [10,19]. Therefore, referral to a gynecologist for assessment and individualized recommendations is mandatory to review the benefits and potential side effects of different contraception methods.

Lastly, suicidal behaviors (other than dialysis withdrawal) have been noted among depressed ESRD patients at higher rates than that is seen among the general population [20,21]. Although preemptive medical treatment termination has not legally been classified as suicide, the influences underlying dialysis treatment termination may be parallel risk factors for suicidal behavior. Our patient started to be noncompliant as regard antihypertensive medication which we consider it as suicidal behavior.

4. CONCLUSION

We believe that fertility is not impossible in HD couples, and it could result in successful pregnancies if the couples were subjected to proper medical and social care. Also,

psychological care is important for the spiritual side of preparing HD patients for pregnancy. If needed, contraception methods must be chosen carefully with a multi-disciplinary discussion between the obstetrician, the patient, the family, and the nephrologist.

CONSENT

Consent was taken from the mother of the patient as the patient died. All data and materials are available.

ETHICAL APPROVAL

The ethics committee in the Central Directorate of Research and Health Development and review in Egypt has approved the study. The committee's reference no. / decision no.: 11-2017/1.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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