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Pregnancy Outcomes in Egyptian Women on Maintenance Hemodialysis: A Multicenter Observational Study

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Authors' contributions

This work was carried out in collaboration among all authors. Research idea and study designed by author AFM, data acquisition by authors GHEK and HEA, data analysis/interpretation authors HFM and EHH; supervision or mentorship author NSA. Author AFM takes 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. All authors read and approved the final manuscript.

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ABSTRACT

Background and Aims: Women in the childbearing period on hemodialysis (HD) have decreased fertility when compared with the general population. However, pregnancy in this patients' population is still possible. The aim of the current study was to assess the conception rate in Egyptian HD females.

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Methods: The study comprises 2 phases: phase one studied the frequency of conception in HD females in Egypt, while phase two studied the live birth frequency and factors affecting it in 22 hemodialysis units (HDUs) including 211 females with sexually active partner in their childbearing period comprising 33 females with HD coincidental pregnancies.
Results: 5-year conception rate was 5.2%, and was associated with higher planned dialysis dose (higher blood flow rate, larger dialyzer size, and session length), better control of blood pressure, as well as a lower level of serum ferritin. Live birth frequency was 33.3% and was statistically significantly associated with younger age of the pregnant lady, higher length of dialysis sessions, lower serum phosphorus level, and suggested better nutrition. There was no maternal mortality associated with HD coincidental pregnancies. There was a better neonatal outcome observed with the caesarian section.
Conclusion: Fertility is possible and safe in Egyptian HD female with a sexually active partner as there is no maternal mortality but not as such for the fetal outcome. Better conception potentials and the outcome are related to better-planned dialysis dosing and adequate control of phosphate and inflammation.

Keywords: Conception; egyptian HD female; HD coincidental pregnancies; mode of delivery; pregnancy outcome.

1. INTRODUCTION

CKD is a global public health problem with an increasing number of its population including those on HD worldwide. In Egypt**,** HD represents the principal modality of management of CKD, and there is a general observation that the fraction of females treated by this modality has been increasing over the last years. Nevertheless, there has been a general concept that women in their childbearing period on HD have decreased fertility when compared with the general population. However, pregnancy in women on HD is still possible [1], although, women who conceive may experience elevated maternal and fetal morbidity and mortality [2,3]. The success of pregnancy may be enhanced by the presence of residual kidney function, improvement of the general health of HD patients, proper control of hypertension with suitable antihypertensive medications, better nutrition, and appropriate correction of anemia. Early identification of the occurrence of pregnancy is of paramount importance as it prompts the attending HD team to improve the quality of dialysis by increasing the dialysis dose and frequency and to implement the appropriate health care steps for a pregnant HD lady. Better fetal outcome has been observed with daily HD sessions [4].

During the past few years, based on the improved awareness of nephrology physicians, the Egyptian government started to fund five to six, instead of three, hemodialysis sessions weekly for HD pregnant ladies to improve fetal outcome. Only a few publications addressed the status of fertility in HD females in Egypt. Thus, it would be interesting to investigate the frequency, consequences of pregnancy in HD females in Egypt and to study factors its success.

The objective of the current work is to assess the frequency of pregnancy in women on HD in Egypt and to study the pregnancy outcome and factors affecting it.

2. METHODS

The present study comprises 2 phases. In the first phase, all the governmental HDUs all over Egypt (n=300) were approached through the usual communication methods such as facsimiles, WhatsApp, and e-mails. A simplified questionnaire was distributed to the HD physicians and staff of as many as possible HD units and was later recollected. This included information on the total number of HD patients, total number of females, number of females with sexually active partners (married females) in the childbearing period (aging 15-50 years), the total frequency of occurrence of pregnancy over 5 years (2011-2016) in each HDU as well as a number of abortions, deliveries, and currently pregnant females. Of the approached HD centers, 291 responded satisfactorily, and these data were used to calculate the frequency of pregnancy-related events.

In the second phase of the study, the more compliant and organized HDUs (n=50) were re-addressed with a more comprehensive questionnaire targeting the females with a sexually active partner in the childbearing period.

Questionnaires of Phases 1 and 2

Pregnancy Sheet – Phase 1 study

*Total count of hemodialysis cases in each unit in the governorate.

*Total count of females in each unit.

*Total count of females at childbearing age (15-50 years) in each unit.

*Total count of married females at childbearing age (15-50 years) in each unit.

*Total count of pregnancies in each unit from 2011 to 2016.

*Total count of miscarriages at the same period.

*Total count of deliveries at the same period.

Send the data within a week to this e-mail: -

Dnps2016@gmail.com

Pregnancy Sheet – Phase 2 study

-Name -Age -Dry body wt

Bl.pr. Pre HD Bl.pr. Post HD Serology Date of start of HD:

-Duration of CKD:

-DM: Yes No -HTN Yes No -IHD Yes No

-No of children -Biggest children -UOP at time of pregnancy

-Age of youngest children -UOP now

-No of sessions / week -CR. Clearance

Duration of each session

BFR

Dialyzer size

-Hb. -Albumin -S.PH -Blurea -URR

-S.Ca -S.Ph -S.K: -TIBC:

-S.ferritin -T.sat -PTH: -Epo dose:

-Iron dose:

-No of pregnancies: Before dialysis -No. of labors :

After start of dialysis -No. of viable fetus:

Purperium :-Postpartum HE

-Fever

-others

Duration of each pregnancy after dialysis in weeks

-Dialysis prescription during pregnancy :- 1st trimaster

-2nd trimaster

-3rd trimaster

-Complications during pregnancy: HTN DM Eclampsia -Fetal outcome: Live Viable baby Still birth Male or female

-Weight of the fetus -Abortion yes or no -Ectopic pregnancy: yes or no

-Menstrual history :- Age of menarch - amount -regular yes or no

-Method of contraception: -Duration of contraception:

-Duration of period

Only twenty-two HDUs from eight governorates responded satisfactorily within 2017 and 2018. The questionnaire of the second phase stressed on data concerning age, history of associated comorbidities, menstrual, obstetric and gynecological history, the HD details and the routine laboratory investigations, and more detailed history concerning females with pregnancy during HD. We defined pregnancy that occurred in women treated by HD in the childbearing period as HD-coincidental pregnancy. The frequency of live birth was calculated by dividing the number of deliveries that resulted in live-born neonates by the total number of pregnancies recorded in the studied group. Regarding live birth, health status, intellectual and school performance, when applicable were followed, through questioning the mothers, till June 2019.

Copies of the two questionnaires are shown.

2.1 Statistical Analysis

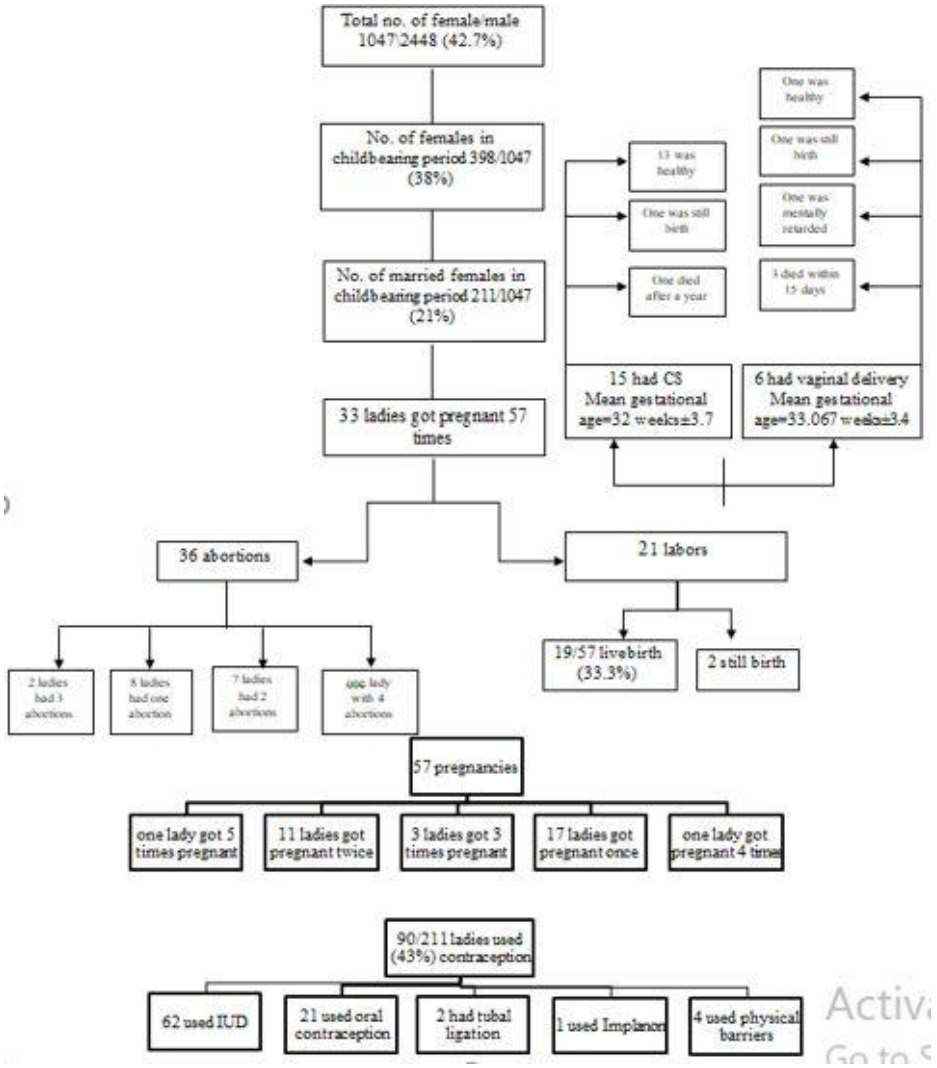
Data were collected, revised, verified then edited on a personal computer and analyzed using IBM SPSS software package version 22.0. Qualitative data were described using numbers and percentages. Quantitative data were described using means and standard deviations for parametric data and medians and interquartile ranges for non-parametric data, after testing normality using Kolmogorov-Smirnov or Shapiro–Wilk tests, as appropriate. The significance of the obtained results was judged at the 0.05 level and all tests were two-tailed. Chi-Square or Monte Carlo tests were used to compare categorical values between different groups as indicated. For comparing differences of continuous variables between two groups, student t-test was used for parametric and Mann-Whitney for non-parametric variables.

3. RESULTS

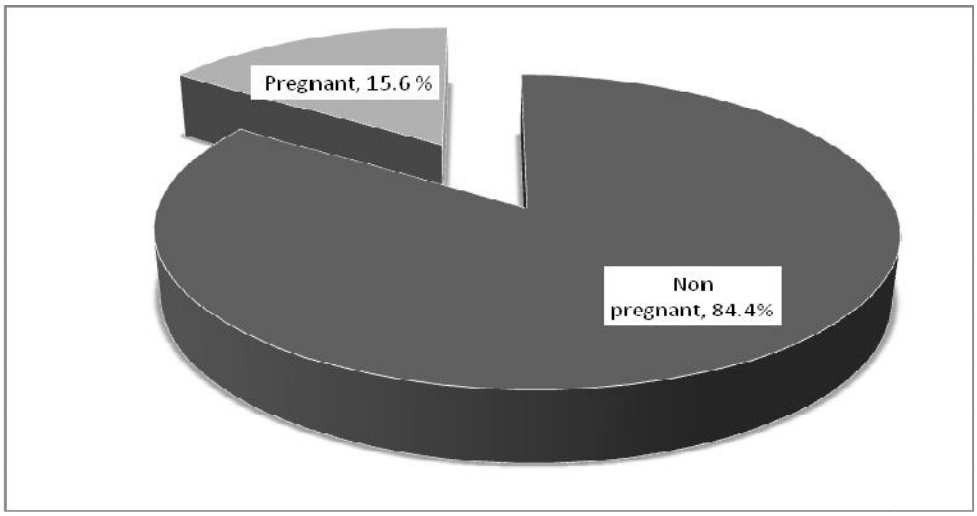
The distribution of the studied HD patients in the 291 surveyed units of phase 1 of the study according to gender, age, frequency of pregnancy, and delivery in the five-year duration of the recall is shown in Table (1). The cumulative frequency of conception over this duration, irrespective of its consequences, was 5.2 % among the total number of married females in the childbearing period. During the 5-year recall period of phase 1 of the study, 37.3%, of pregnancies resulted in a live birth, 56.99% resulted in abortion while the remaining ~6% of them were still pregnant at the time of phase-1 questionnaire (Table 1).

Table 1. Distribution of Egyptian HD patients according to gender, age, frequency of pregnancy, and delivery in a five-year duration

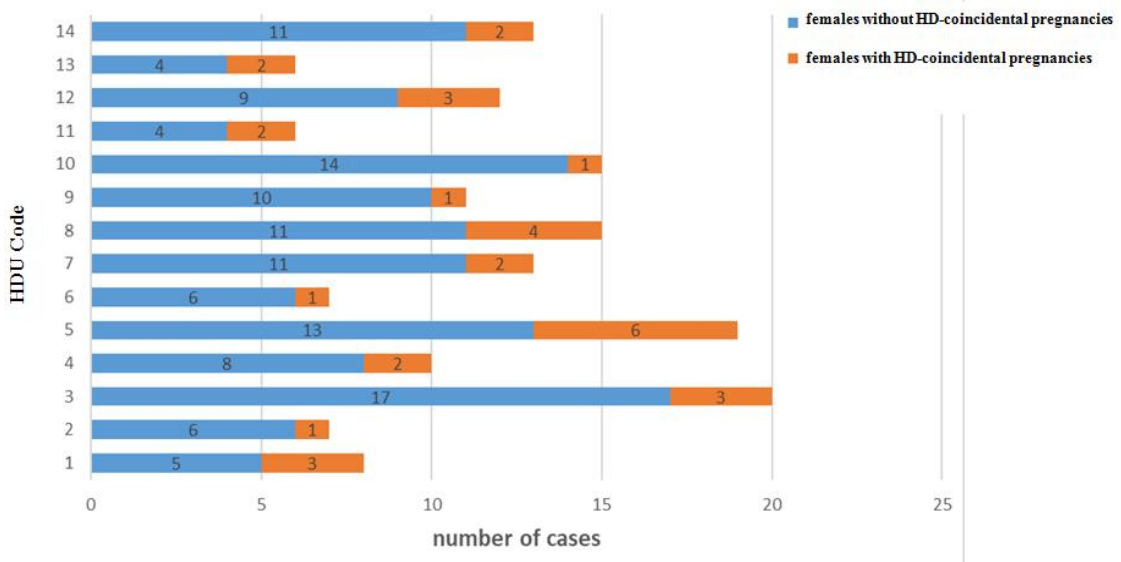
Participating governorates	26
Participating units	**291**
Total no of Patients in June 2016	**25381** **Males:** 16373 **Females:** 9890
No. of all females according to age	**0-15 yrs: 8** **15-50 yrs: 4472** **>50 yrs: 5410**
Total no of Females in child bearing period	with a sexually active partner**: 3714** without a sexually active partner**: 758**
Total no. of Pregnancies within 5 years (2011-2016)	**193** **Abortions:** 110 (57%) **Delivery:** 72 (37.3%) **Still pregnant: 11 (5.7%)**
Five years conception rate	**5.2 %**



Graph 1. Distribution of pregnancy and its fate in 33 ladies in phase two



Graph 2. Percentage of females with HD-coincidental pregnancies to the whole studied group



Graph 3. Number of females with HD-coincidental pregnancies in relation to the total number of married females in the childbearing period in the same 14 HDUs

The total number of patients in the twenty-two HDUs participating in phase 2 of the study was 2448. Females constituted 1047; 211 were married and in the childbearing period at the time of the study. Only thirty-three ladies (15.6%) dialyzing in fourteen HDUs experienced fifty-seven pregnancies during their whole HD duration, of which 33.3% (19 out of 57) were live births and 63.1% (36 out of 57) were abortions while the remaining two were stillbirth Graph (1). Graph (2) shows the percentage of females with HD-coincidental pregnancies in the whole studied group.

The percentage of pregnancy to the total number of females with a sexually active partner in the childbearing period in each of the fourteen HDUs is shown in Graph (3).

The study showed no pregnancy-related maternal mortality over the course of the fifty-seven pregnancies. Mothers' age ranged from 24 to 50 at the time of the study. The younger the mothers, the higher the chance for near term pregnancies and escaping abortion. Among the viable babies; the mean fetal weight was 2.1 kg (median fetal weight is 1.95 kg, and ranged between 0.9 – 3.5 kg). The mean gestational age

32.6 weeks with a range 24 – 36 and median 34 weeks (data not shown).

Fifteen of the twenty-one deliveries were accomplished through caesarian sections (CS); resulting in fourteen live-births and one still-birth, while six ladies delivered through the vaginal route, resulting in five live-births and one still-birth. Of the nineteen live-birth cases, three newly born babies died within 15 days and one infant died at the age of one year; the remaining fifteen were still alive till the end of June 2019. By the latter date, the youngest surviving offspring had aged nine months and the oldest ten years. Except for the latter child who suffers from mental retardation, all were in good health. Three live births died within four up to fifteen days following delivery while in the neonatal intensive care units (NICU). Graph 1 shows the flowchart of the pregnancy fate observed in the study.

Tables (2A) and (2B) show the relation between the length of dialysis sessions on one hand, and on the other hand pregnancy outcome, delivery outcome, gestational age, and offspring health status, respectively. Most of the females with successful pregnancies received four to six HD sessions weekly (20-24 hours /week) once pregnancy was diagnosed. One female who was known to pass a reasonable amount of urine output received HD 12 hours/week and delivered a live birth baby at 35 weeks' gestational age. Unfortunately, this baby died after 15 days whilst in the NICU. (data not shown). Twenty hours' session duration per week was provided to nine pregnancies, while eleven pregnancies were provided with twenty-four-hour sessions per week. Mean gestational ages were 31.78 vs. 33.36 for the HD-coincidental pregnancies dialyzed twenty and twenty-four hours, respectively; a difference that is not statistically significant.

Females who reached delivery had a mean age that is statistically significantly lower than those who experienced abortions. In addition, lower mean serum phosphorus appeared to be higher in patients who experienced abortion than those who reached delivery; although the difference is not statistically significant Table (3).

The married females in the child-bearing period in the study (n=211) were sub-grouped according to their last available systolic and diastolic blood pressure measurements into two sets three tertiles and these tertiles were compared regarding the frequency of HD-coincidental pregnancies Table (4). There is no statistically significant difference however there is a higher frequency of females with HD-coincidental pregnancies with lower diastolic and systolic blood pressure.

Table 2A. Relation between the length of dialysis sessions and pregnancy outcome

Number of Cases in Each Trimester	**Delivery (21)**				**Abortion (36)**			
	12 hrs N=21(%)	16 hrs	20 hrs	24 hrs	12 hrs N=7(%)	16 hrs	20 hrs	24 hrs
Length of duration session in 2nd trimester	1 (4.8)	2 (9.5)	8 (38.1)	10 (47.6)	0 (0.0)	5 (71.4)	2 (28.6)	0 (0.0)
	N=21(%)				N=0(%)			
Length of duration session in 3rd trimester	1 (4.8)	0 (0.0)	9 (42.9)	11 (52.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 2B. Relation between the length of dialysis sessions, delivery outcome, and offspring status

Length of dialysis sessions in 3rd trimester	**20 hrs. N=9**	**24 hrs.N=11**	
Delivery outcome			
***Still birth**	2 (22.2%) (24, 30 weeks)	0	FET , P=0.19
Died within 15 days		2 (18.1%)	
Died after one year		1 (9.09%)	
Mentally retard		1 (9.09%)	
Healthy	7 (77.8%)	7 (63.63%)	
Mean gestational age in weeks (Std)	31.78 (4.15)	33.36 (2.81)	P=0.32

**P= student t test FET: Fischer exact test*

Table 3. The relation between demographic and laboratory data and Fate of pregnancy in the studied 33 ladies during HD

Clinical data				
		Females who experienced delivery during HD	**Females who experienced abortion during HD**	**P**
Age	N Mean (SD) Min-max	16 35.4 (5.9) 27-48	17 41.6 (4.27) 32-50	0.002
Dry body weight	N Mean (SD)	16 66.5(14.17)	17 66.75(15.86)	0.971
Blood flow rate	N Mean (SD)	16 302.94(27.78)	17 312 (28.33)	0.369
Dialyzer size	N Mean (SD)	16 1.48 (0.16)	16 1.44(0.1)	0.405
Lab Data				
		Delivery	**Abortion**	**P**
Hb	N Mean (SD)	15 9.3(1.3)	15 9.5(1.63)	0.714
Serum Albumin	N Mean (SD)	10 3.87(0.41)	14 3.8(0.52)	0.728
Serum Calcium	N Mean (SD)	14 8.39 (0.86)	15 8.38(0.692)	0.965
Serum Phosphorus	N Mean (SD)	14 4.7429(1.32)	15 5.4(1.75)	0.268
Parathyroid hormone level	N Mean (SD) Median (IQR)	7 542.44 (324.54) 451.3 (380 – 827)	6 578.88 (614.82) 365 (132.82 – 1016.5)	0.894
Serum ferritin	N Mean (SD) Median (IQR)	7 676(571.7) 500 (362 – 850)	11 555.21 (586.73) 445 (131 – 699.9)	0.673
Serum Potassium	N Mean (SD)	7 4.65 (0.93)	12 4.6(0.72)	0.884
Avg. DBP	N Mean (SD)	15 80(10.177)	16 75.6250(7.5)	0.182
Avg. SBP	N Mean (SD)	15 128.33 (18.77)	16 121.56 (16.09)	0.289

N= Number of available data

Table 4. Frequency of pregnancy in relation to tertiles systolic then diastolic blood pressure

		Highest tertile	Middle tertile	Lowest tertile	P
Diastolic blood pressure	N Range of DBP Frequency of pregnancy	64 85.0-110.0 7/64(10.9%)	64 75.0-85.0 9/64(14.1%)	65 55.0-75.0 15/65(23.1%)	0.066
Systolic blood pressure	N Range of SBP Frequency of pregnancy	62 135-200 7/62(11.3%)	62 120-135 11/62(17.7%)	61 90-120 13/61(21.3%)	0.134

Table 5. Comparison between HDUs with females with HD-coincidental pregnancies and HDUs with females without HD-coincidental pregnancies

Dialysis characters among HDUs without pregnant females and HDUs with pregnant females				
		Females in 8 HDUs without HD-coincidental pregnancies (n=49)	**Females in 14 HDUs With HD coincidental pregnancies (n=162)**	***P***
Age/years	Mean±SD	37.7±6-.62	9.34±6.96	P=0.15
BMI(Kg/m2)	N* Mean±SD	9 27.23 ± 8.2	13 28.36±3.97	 p=0.31
Sessions duration	Mean±SD	3.99±0.07	3.98±0.11	p=0.89
Blood flow rate	Mean±SD	284.7±24.9	304.9±21.1	p<0.001*
Dialyzer size	Mean±SD	1.4±0.14	1.46±0.16	p=0.02*
Duration of dialysis in months	N* Median(IQR)	49 35(15-65.5)	141 53(26-97.5)	 p=0.009*
Medical history and vital signs				
		N (%)	N (%)	
DM		3(6.1%)	13(8.1%)	FET P=0.76
Hypertension		24(48.9%)	90(56.2%)	χ^2=0.88 P=0.35
IHD		4(8.2%)	13(8.1%)	FET P=1.0
DBP	N* Mean±SD	42 89.29±22.7	153- 75.95±10.1	 p<0.001*
SBP	N* Mean±SD	42 135.9±25.67	153 133.76±25.02	 p=0.62
Duration of dialysis in months	N* Median(IQR)	49 35(15-65.5)	141 53(26-97.5)	 p=0.009*

Dialysis characters among HDUs without pregnant females and HDUs with pregnant females				
		Females in 8 HDUs without HD-coincidental pregnancies (n=49)	**Females in 14 HDUs With HD coincidental pregnancies (n=162)**	***P***
The gynecological and obstetric history				
Age at menarche /years	N* Mean±SD	35 11.71±1.66	82 12.07±1.51	t=1.15 p=0.45
Menstruation pattern N*		=46 N (%)	N=131 N (%)	MC p=0.04*
Regular		43(93.5%)	101(77.1%)	
Menstruation duration	N* Mean±SD Median (IQR)	35 4.66±1.6 6.0(4.0-10.0)	117 4.62±1.9 4.0(1.0-7.0)	P=0.93
Laboratory tests				
HB (gm/dl)	N* Mean±SD	38 8.52±1.56	150 9.40±1.7	p=0.003*
Albumin	N* Mean±SD	30 3.63±0.52	105 3.69±0.56	p=0.55
Serum creatinine	N* Mean±SD	9 8.45±1.2	27 6.3±2.14	p=0.007*
Serum calcium	N* Mean±SD	35 8.78±1.5	131 8.39±0.77	p=0.22
Serum phosphorus	N* Mean±SD	39 5.41±1.67	126 4.87±1.60	p=0.07
Serum K	N* Mean±SD	16 4.8±0.78	75 4.94±0.92	p=0.56
URR	N* Mean (Std. Deviation)	35 0.6211(0.09964)	102 0.6425(0.08992)	p=0.24
Parathyroid hormone level	N* Median (IQR)	16 433.0(402.5-666.72)	59 480(216.0-565.0)	p=0.09
Serum ferritin	N* Median (IQR)	18 379.5(187.5-545.9)	89 630(379.9-1006.5)	p=0.01
T.sat	N* Median (IQR)	11 22.0(20.0-25.0)	83 27.0(18.15-37.0)	p=0.29

N= Number of available data*

Table 6. Comparison between females with HD-coincidental pregnancies and those without within the same HDUs with females with HD-coincidental pregnancies

Demographic data in HDUs with females with HD-coincidental pregnancies				
		HD-coincidental pregnancies HDUs		test of significance
		females without HD-coincidental pregnancies n=129	females with HD-coincidental pregnancies n=33	
Age/years	Mean±SD	39.6±7.2	38.31±6.01	p=0.35
Serology		N*=113	N*=33	
		N (%)	N (%)	MC
Hcv positive		30/129(23.25%)	10/33(30.3%)	P=0.84
Hcv and Hbv positive		1(0.77%)	0	
Diastolic Blood Pressure	Mean±SD	76.31±10.1	74.52±9.9	p=0.38
Systolic Blood Pressure	Mean±SD	135.3±26.4	127.7±17.8	p=0.13
Dialysis characters and medical history in studied groups				
Sessions duration	Mean±SD	3.98±0.12	4.0±0.0	p=0.48
BFR	Mean±SD	304.3±19.14	307.19±27.9	p=0.49
Dialyzer size	Mean±SD	1.46±0.17	1.46±0.14	p=0.87
Duration of Dialysis in months	N*	113	28	
	Mean±SD	60.49±48.5	93.43±49.4	p=0.002*
		N=127	N=33	
		N (%)	N (%)	
DM		9(69.2)	4(30.8)	χ^2=0.89 p=0.35
Hypertension		71(78.9)	19(21.1)	χ^2=0.02 p=0.89
IHD		12(92.3)	1(7.7)	χ^2=1.45 p=0.23
The gynecological and obstetric history between studied groups				
Number of children	N	126	33	
	Median (IQR)	2.0(1.75-3.0)	2(2.0-3.0)	P=0.58
Age at menarche	N	65	17	
	Median (IQR)	12.0(11-13)	13(11.5-14)	p=0.03*
Menstruation pattern		N*=102	N*=29	
		N *(%)	N *(%)	MC

Demographic data in HDUs with females with HD-coincidental pregnancies				
		HD-coincidental pregnancies HDUs		test of significance
		females without HD-coincidental pregnancies n=129	females with HD-coincidental pregnancies n=33	
Regular		78(76.4)	23(79.31)	P=0.56
Menstruation duration	N*	93	24	
	Mean±SD	4.55±1.9	4.92±1.8	p=0.40
	Median (IQR)	4.0(1.0-7.0)	3.0(0.75-7.5)	
Number of pregnancies before	N*	125	31	
	Median (IQR)	3.0(2.0-4.0)	2.0(1.0-5.0)	p=0.72
Number of deliveries before HD	N*	33	33	Z=1.14
	Median (IQR)	2.0(2.0-3.0)	2.0(2.0-4.0)	P=0.26
Laboratory characteristics between studied groups				
HB	N*	120	30	
	Mean±SD	9.36±1.8	9.4±1.5	p=0.9
Albumin	N*	81	24	
	Mean±SD	3.66±0.58	3.83±0.47	p=0.12
Serum creatinine	N*	22	5	
	Mean±SD	6.25±2.3	6.5±1.5	p=0.82
Serum calcium	N*	102	29	
	Mean±SD	8.53±1.1	8.39±0.77	p=0.51
Serum phosphorus	N*	97	29	
	Mean±SD	4.81±1.6	5.08±1.6	p=0.43
URR	N*	78	24	
	Mean (Std. Deviation)	0.6471(0.08691)	0.6275(0.09958)	p=0.35
PTH	N*	46	13	
	Median (IQR)	351.65(213.3-538.8)	430.0(224.0-803.0)	p=0.37
Serum ferritin	N*	71	18	
	Median (IQR)	680.0(399.0-1112.1)	472.5(311.5-707.4)	p=0.08
T.sat	N*	67	16	
	Median (IQR)	27.0(17-37.56)	27.8(18.61-36.25)	p=0.84
S potassium	N*	56	19	
	Median (IQR)	5.0(4.43-5.2)	4.6(4.0-5.3)	p=0.18

N= Number of available data, MC: Monte Carlo test, p: probability *statistically significant (p<0.05), t: Student t test Z: Mann Whitney U test χ^2=Chi-Square test, IQR: Interquartile range, SD: Standard deviation*

Table (5) shows a comparison between the HDUs serving females with HD-coincidental pregnancies and those with no pregnancy as regard dialysis characteristics, medical history, gynecological and obstetric history, and laboratory variables. The dialysis sessions in the units serving females with HD-coincidental pregnancies had statistically significant higher blood flow rates, larger dialyzer sizes, a longer length of dialysis sessions, lower diastolic blood pressure, and less regular menstruation compared to the units which served females without HD-coincidental pregnancies. On the other hand, blood hemoglobin and serum ferritin levels were significantly higher in the former than those in the latter units, while the other laboratory variables did not show the difference between the two sets of HDUs.

Comparisons between females with, and those without, HD-coincidental pregnancies within the set of fourteen units that served ladies with HD-coincidental pregnancies, as regards demographic data, medical history, gynecological and obstetric history, dialysis characters, and laboratory data are shown in Table (6). There was a statistically significant older age of menarche (but still in the average range), and a lower frequency of regular menstrual cycle in females with than those without HD-coincidental pregnancies. Conversely, there was no statistically significant difference between both groups in all lab parameters.

4. DISCUSSION

The first pregnancy with a successful outcome in a patient on HD was described in 1971[5]. Pregnancies in dialysis patients are uncommon and difficult to study as the majority of nephrologists encounter one or two pregnant patients during their time in practice [4]. The percentage of successful pregnancies has increased consistently, but there is still a high fetal mortality and morbidity rate as compared to the normal population [6].

The objectives of the current study are to assess the frequency of pregnancy in women on HD in Egypt, to study fertility of HD females with sexually active partners in the childbearing period, pregnancy outcome, and factors affecting both, and to recognize the characteristics of females with HD-coincidental pregnancies. The study comprises 2 phases.

The frequencies of conceptions reported in the various studies are different from one area to another and do not present a particular trend over time, maybe due to a lack of uniformities of design in many studies. The results of phase 1 of the current study showed the cumulative conception rate in married female in childbearing period equals 5.2% over a 5-year duration, which is in concordance with the data reviewed by Hou S who stated that the frequency of conception among ESRD patients of childbearing age on dialysis is nearly 1.5 conceptions per 100 patients per year in the USA, in the eighties and nineties [7]. Similarly, Manisco G et al reported that the incidence of pregnancy ranges from <1% to approximately 7% [8]. The Australian and New Zealand Dialysis and Transplantation Registry from 2001 to 2011 reported seven conceptions per year (8.4 pregnancies in 1000 patient-years at risk) [9]. Furthermore, in dialysis patients, pregnancy might have been frequently diagnosed so late that early losses were unlikely to be properly accounted for in the registries; in fact, the diagnosis was documented to be delayed into the second trimester in many reports [10 and11]. Thus, the possibility of missing at least the unnoticed conception might constitute a major limitation in the accurate estimation of the rate of conception in these populations.

Better dialysis parameters (higher blood flow rate, bigger dialyzer size, longer HD sessions duration, and lower serum phosphorus) and also better anemia status and lower level of blood pressure were observed in HDU containing HD coincidental pregnancies than HDU without. While nearly there is no difference as regard dialysis parameters anemia status and blood pressure level within the same HDUs whether the female got pregnant during HD or not. This is supported by many studies that suggested that improvement of fertility in HD patients over time is probably related to the widespread use of erythropoietin stimulating agents and more intensive HD regimens and current advances in anti-hypertensive therapy. The innovations in HD are reflected in increased pregnancy rates over time and have been described in data from the United States [12], Canada, [2], and the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry [13].

Serum ferritin was significantly lower in females who got HD coincidental pregnancies. Serum ferritin, which acts as an inflammatory marker, might be a limiting factor for conception in HDUs. Serum ferritin values in the range of 200–2000 ng/ml may be increased due to non-iron-related

factors including elements of malnutrition–inflammation complex syndrome [14]. In addition, Kell DB et al stated that the level of serum ferritin correlates with numerous inflammatory and degenerative diseases [15].

Piccoli GB et al reported in a nationwide survey including 20 mothers on HD and 3 on peritoneal dialysis that the gross mortality of mothers was not different from that expected in young dialysis populations (1.5 per 100 years of observation) [16]. They found that there is no additional risk for HD females who experienced pregnancy during HD. This also was evident in our data where there was no reported maternal mortality.

Minor differences that appeared in live birth frequency between phase two and one in the current work (33.3% - 37.3% respectively) may be attributed to more detailed history collected in phase two as regard pregnancy outcome. This copes with the international data published before the 1990s as supported by Manisco G et al who reviewed percentages of miscarriage which was 70% before 1990 and less than 40% in the following years. Moreover, the other reviewed studies showed different live birth frequencies ranged from 52-70% of cases [17,18 and 19]. Our explanation as regard lower live birth frequency in the current study might be attributed to many factors that could affect the pregnancy fate and offspring outcome. Firstly, nutritional status might affect the fetal outcome. But the nutritional status of the patients was not investigated properly. Serum albumin showed an average of 3.7 gm/dl in the total studied group while it ranged from 3.1 – 5 gm/dl in females with HD-coincidental pregnancies. Vidal ML et al describes their experience in the follow-up of four patients with chronic renal failure who became pregnant while being treated with chronic HD [20]. The outcomes were successful and each gave birth to healthy babies. The adequate nutritional condition previous to the pregnancies added more safety to their management. Special dedication to the nutritional control enabled a good outcome of their pregnancies.

Secondly, most of the studied patients in the current work who experienced pregnancies during HD were subjected to intensive twenty to twenty-four hrs HD per week during pregnancy. Twenty-two percent of pregnancies that received a dialysis dose of twenty hrs /week resulted in stillbirth with a lower mean gestational age of live birth, while all pregnancies that received Twenty-four hours/week HD got live birth. This is in agreement with various studies. Villa G et al reported that, after a gestational age of 16–20 weeks, HD dose should be increased from 3–4 sessions/week to daily sessions and better fetal outcomes are obtained with an HD schedule of 24–28 h/week [21]. Additionally, the live birth frequency was 48% in women receiving 20 h of HD per week or less, and 85% in women receiving 36 h of dialysis per week or more [22]. In Egypt, in the past, the cost of HD sessions more than 3 sessions per week might be a detrimental factor in the intensification of HD doses once pregnancy is diagnosed. While recently governmental account affords the cost of six sessions per week for pregnant ladies on HD which may improve the live birth frequency and offspring outcomes in the future.

Thirdly, data of the current work showed mean age±SD 35.4±5.9 yrs in females who experienced delivery vs. 41.6±4.27 yrs in females who experienced abortion. This is supported by Kushner DH who suggested that pregnancy after 45 years is infrequent and the mother and the baby should be considered as high risk and there is a greater incidence of spontaneous abortion, gestational trophoblastic disease, and chromosomal abnormalities in the fetus [23]. On contrary, Manisco G et al declared that there is no significant data about the impact of maternal age or type of nephropathy on the pregnancy outcome or maternal/fetus prognosis in pregnancies that occurred in dialysis patients [8].

Fourthly, longer dialysis duration was observed in females who got HD coincidental pregnancies and this might be a limiting factor of lower live birth frequency in the studied group which might be due to loss of residual kidney function after a long period of dialysis and also vascular calcification that could occur in uterine vessels. In a parallel context, Jesudason S et al found that women with kidney disease who start chronic dialysis after conception have superior live birth frequencies compared with those already established on dialysis at the time of conception, although these pregnancies remain high risk [9].

Finally, serum phosphorus was lower in patients who experienced delivery than those who experienced abortion, although it is not statistically significant. This could be a marker of better dialysis dose and could represent less risk of occurrence of vascular calcification.

The current study showed 100 % preterm delivery and also showed CS being performed in 71.15%with mean gestational age 32.6 weeks. This finding copes with many of the international studies; Bagon JA et al reported the incidence of low birth weight and prematurity were 100%, and CS was performed in 66% of successful pregnancies [24]. Giatras I et al reported mean gestational age at delivery 30.5 weeks in their study [25]. While Jesudason S et al observed a median gestational age of 33.8 weeks with a median birth weight of 1750 gm [9]. Piccoli GB et al concluded that longer weekly dialysis times were associated with lower rates of preterm delivery and small for gestational age offspring [26].

General practice between obstetricians considers CS the safest method for delivery in preterm deliveries especially if it occurred in patients with chronic disease especially HD patients. Although this practice had the upper hand for decades but still lacking evidence that CS is safer for the mother and the neonate [27]. However, CS secured preterm babies from intracranial hemorrhage that might associate compression-decompression with vaginal delivery. On the other hand, Hogberg U et al evidences that CS delivery benefits the preterm infant is lacking [28]. Planned cesarean delivery for women thought to be in preterm delivery may be protective for the baby, but could also be quite traumatic for both mother and baby. The optimal mode of delivery of preterm babies for both cephalic and breech presentation remains, therefore, controversial [29]. Putting into consideration that vaginal delivery promotes the production of various cytokines and their receptors, which are implicated in neonatal immunity [30]. However, many international studies preferred CS as a mode of delivery for pregnancies in HD patients (more than 50 % of their cases) [19,31,32]. Gestational age of all delivered babies ranged from 24 -36 weeks in the current data and the live birth delivered by CS had better neonatal outcomes, but still mode of delivery needs further studies.

This work showed 9.5% of the total birth born stillbirth, 4.5% died after one year due to unknown cause, 4.5% mentally retarded and 14% died during admission to NICU. We could assume these partially to prematurity and suspected improper neonatal care. Premature delivery is almost invariable and is the most common cause of pregnancy loss. Chow Y et al reported that preterm birth is the single most important determinant of adverse outcomes in terms of survival [33]. Those premature without a disability have a two-fold or greater increased risk for developmental, cognitive, and behavioral difficulties [34,35]. Hou S stated that the availability of a high-risk obstetrician and a nursery capable of caring for extremely premature infants is important for a successful pregnancy outcome [36]. Antenatal monitoring of fetal well-being is usually started as soon as babies are viable. Most babies born to dialysis patients require a neonatal intensive care unit because of prematurity. Even those born close to term should be monitored closely because they generally have a solute diuresis and may become seriously volume-contracted.

Ovarian aging in women of childbearing periods who are HCV+ is associated with a lower chance of live birth, greater risk of infertility, gestational diabetes, pre-eclampsia, and miscarriage. Such risks could be positively influenced by a successful HCV cure [37]. This is in contrary to our findings as the frequency of pregnancy in HCV +ve antibody patients is comparable to its frequency in HCV -ve antibody patients which suggests that HCV might not affect fertility in HD patients and could be attributed to the less reliable diagnosis of HCV +ve patients in our HDUs as it is based on HCV antibody screening by ELISA technique rather than PCR. Comparing EIA and PCR methods reveals that rates of false positive and false negative results were higher with the EIA method [38].

There was poor response regarding some points in the phase 2 questionnaire of the study, particularly those concerning sexual relationships in HD females, lab data related to dialysis adequacy (KT/V). and requested a 24-hour urine output. In addition, there are only 1 to 3 cases that get pregnant within most of the HDUs containing HD-coincidental pregnancies. This situation limits gaining skills. Also, our pregnant ladies were not investigated during the duration of their pregnancies. However, the strengths of the study include: it is carried out on a large scale with highlights on the live-born babies and offspring status. Nearly, it is the first study performed in Egypt searching for conception rate and live- birth frequency in HDUs as a multicenter study.

5. CONCLUSION

Pregnancy is not uncommon in Egyptian HD females with a sexually active partner. Better control of blood pressure and higher dialysis dose with lower serum ferritin are associated with

higher chances to get pregnant successfully. HD-coincidental pregnancies did not affect maternal mortality. The lower age of the pregnant female was associated with better pregnancy outcomes, and more frequent and prolonged dialysis session time are associated with longer gestational age, less frequency of abortion, and better pregnancy outcome. CS might be preferred for a better neonatal outcome.

The abstract of the manuscript is accepted as a poster presentation in the International Society of Nephrology 2020 conference.

6. LIMITATIONS OF THE STUDY

Data including partner health status, socioeconomic status, and employment status as well as whether pregnancies were planned or not are collected as part of the registry.

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CONSENT AND ETHICAL APPROVAL

Ethical Committee Approval: Depending on Egyptian minister of health and population decree #95/year 2005 for Health Research and decree #539/year 2016 – ICH – Good Clinical Practice, Declaration of Helsinki and World Health Organization Guidelines, the Ethics Committee meeting in the Central Directorate of Research and Health Development and review: Pregnancy Outcomes in Egyptian Women on Maintenance HD: A Multicenter Observational Study. The approval number is Com. No/Dec. No: 11-2017/ 1, Moreover, Verbal consent was taken from all the participants.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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