Pregnancy in Dialysis Patients: Is the Evidence Strong Enough to Lead Us to Change Our Counseling Policy?

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Background and objectives: Although successful pregnancy is rare, results attained with higher dialysis efficiency and the spread of dialysis to different cultural and religious settings are changing the panorama. In this study, we systematically review the recent literature (2000 through 2008) on pregnancy in dialysis.

Design, setting, participants, & measurements: Medline on OVID was searched in November 2008, with MESH and free terms on pregnancy and chronic kidney disease or dialysis; limits were human subjects and English-language articles. Case reports were excluded to minimize publication bias. The final selection and extraction of data were performed in duplicate.

Results: From 2840 references, 241 full-text articles were retrieved; eight fulfilled the selection criteria, and two were added from reference lists. In the 10 studies (nine of 10 monocentric), 90 pregnancies were observed in 78 patients (range of cases five to 15). The studies were heterogeneous for definition of outcomes, duration (2 to 16 yr), period (1988 through 1998 to 2000 through 2006), age (25 to 35 yr), and support and dialysis therapy. Daily dialysis was frequently used; type of treatment, membranes, and flows varied widely. Hypertension and anemia were frequent concerns for the mothers. Intrauterine deaths, hydramnios, and small-for-gestational-age or preterm infants were frequent. The possibility of a healthy offspring ranged from 50 to 100% (overall 76.25%).

Conclusions: Evidence on pregnancy in dialysis is heterogeneous; however, the growing number of reports worldwide and the improving results suggest that we should reconsider our counseling policy, which only rarely includes pregnancy in dialysis patients.

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Almost 40 yr after the first report of a successful pregnancy in a dialysis patient by Confortini *et al.* (1), many issues concerning pregnancy in dialysis patients are still unresolved. Over time, the results of pregnancy in dialysis display an improving trend, with roughly a 25% fetal survival gain per decade. In 1980, the European Dialysis and Transplant Association reported that only 23% of 115 pregnancies in dialysis ended with surviving infants (2). In 1998, Bagon *et al.* (3) described a national survey showing a successful outcome in approximately half the pregnancies of dialysis patients. There are few case series in the new millennium, mainly from single experienced centers, many of which report a successful outcome rate of >70% (4,5).

Despite the improving results, pregnancy in long-term dialysis patients is often considered a challenging but rare and almost exceptional situation, which occurs unexpectedly in the majority of the women (6). The cause of this widespread opinion is the generally reduced fertility in dialysis patients. Anemia and hyperprolactinemia are considered the major—but not the only—determinants of loss of menses and anovulatory cycles. Polypharmacy may play an important role. Depression; loss of sexual desire; and, particularly in Western society, which tends to discriminate patients with chronic diseases, frequent difficulties in marital life may significantly add to the picture (6). Furthermore, the idea that transplantation, by restoring fertility and recovering near-normal renal function, is the best way to allow a woman with uremia to conceive may have led us to ignore the problem of pregnancy in female dialysis patients. The nihilistic outlook of discouraging pregnancy in dialysis patients has recently been challenged by several considerations (6). Even though kidney transplantation is universally considered the number 1 therapy for young patients with ESRD, a never-ending lack of donor organs and the consequently long waiting lists may hinder the possibility of receiving a kidney in time to become pregnant (6).

Dialysis is becoming a possible treatment in more and more countries. There is a growing number of reports on pregnant dialysis patients from countries where cultural habits and religious beliefs strongly support a central role of large families, an outlook very different from that in most European and North American countries (7–10). Furthermore, the greatly improved results attained with higher dialysis efficiency may contribute to a different outlook with respect to pregnancy in dialysis (5).

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Table 1. Main features of the studies

Reference	Period of Study	Country	Type of Study	Objective as Stated in the Study	No. of Cases	Maternal Age
Chou *et al.* (9), 2008	1990 to 2006	Taiwan	Ret	To investigate the pregnancy outcome in patients on chronic dialysis over the past 15 yr in a single center and also perform a combined analysis of results . . . from reported series to obtain overall estimates of rates of successful delivery	13 P[a]	HD group: 35.0 ± 4.3
Bamberg *et al.* (15), 2007	2000 to 2004	Germany	Ret	To evaluate the effect of intensified fetal surveillance *via* Doppler ultrasound and fetal nonstress test on the perinatal outcome of pregnant women on an intensified hemofiltration scheme	5 P[b]	28 (21 to 37)
Barua *et al.* (5), 2008	2001 to 2006	Canada	DCS M	To describe maternal and fetal outcomes as well as changes in clinical and biochemical indices before and after conception	7 P, 5 W[c]	33 ± 4
Tan *et al.* (16), 2006	1995 to 2004	Singapore	Ret	To report obstetric outcomes in women undergoing chronic renal dialysis	11 P, 7 W[d]	28 (25 to 39)
Malik *et al.* (8), 2005	1992 to 2003	Saudi Arabia	Pro	To report the frequency and outcome of pregnancies of women on dialysis in a referral center in Saudi Arabia	12 P, 9 W[e]	29 (20 to 37)
Haase *et al.* (17), 2005	2000 to 2004	Germany	Pro	To report the successful multidisciplinary management of five consecutive pregnant dialysis patients	5 P[f]	28.0 ± 6.6
Eroğlu *et al.* (7), 2004	2000 to 2002	Turkey	Ret	To review the treatment and outcome of seven pregnancies in women undergoing chronic hemodialysis	7 P[g]	25 (22 to 31)
Moranne *et al.* (18,29), 2004	1995 to 2001	France	NR	Not specified (letter)	7 P[h]	NR
Luciani *et al.* (19), 2002	1988 to 1998	Italy	Ret	To review the patients on hemodialysis to identify the factors that may affect the course of the pregnancy and the fetal outcome	5 P[i]	27.00 ± 3.46
Chao *et al.* (12), 2002	1990 to 2000	Taiwan	Ret	To describe the treatment of pregnancy and the outcome in a series of patients undergoing long-term hemodialysis	18 P, 15 W	29 (22 to 43)

Ret, retrospective; DCS, descriptive cohort study; Pro, prospective; NR, not reported; M, multicenter; P, pregnancies; W, women.

[a]Underlying causes: Chronic glomerulonephritis (CG), 5; systemic lupus erythematosus (SLE), 3; rapidly progressive glomerulonephritis, 1; preeclampsia (PE), 1.

[b]Focal segmental nephritis, 1; Lignac-Fanconi syndrome, 1; poststreptococcal glomerulonephritis, 1; mesangioproliferative glomerulonephritis, 1; amyloidosis, 1.

[c]Polycystic kidney disease (PKD), 1; IgA nephropathy, 1; calcineurin inhibitor toxicity, 1; hypoplastic kidney, 1; unknown cause, 1.

[d]SLE, 3, ischemic heart disease, 1; parathyroid adenoma, 1; inferior vena cava thrombosis, 1; tuberculosis, 1.

[e]SLE, 2; bilateral small kidneys, 2; reflux nephropathy, 1; chronic pyelonephritis, 1; crescentic glomerulonephritis, 1, FSGS, 1; hemolytic uremic syndrome, 1.

[f]Focal sclerosing poststreptococcal glomerulonephritis, 11; Lignac-Fanconi syndrome, 1; poststreptococcal glomerulonephritis, 1; mesangioproliferative glomerulonephritis, 1; amyloidosis, 1.

[g]CG, 4; interstitial nephritis, 3.

[h]Not specified (letter).

[i]Autosomal dominant PKD, 2; membranoproliferative glomerulonephritis, 1; reflux nephropathy, 1; unknown cause, 1.

Table 2. Control policies

Reference	Dialysis	Control Policies: Infants	Control Policies: Fetal Monitoring (as Specified in the Articles)	Control Policies: Other (as Specified in the Articles)
Chou *et al.* (9), 2008	HD and PD	Followed by pediatricians for 2 yr	Not specified (retrospective analysis of clinical charts)	Biochemical tests before and after dialysis
Bamberg *et al.* (15), 2007	HD	Followed up to preparation of this report	Fetal monitoring started immediately after confirmation of conception. Ultrasound examination at beginning and end of each dialysis session. Sonographic measurement of cervical length (weekly). After 25 wk, fetal monitoring by cardiotocography (twice a week to daily) and weekly measurement of the Doppler flow in the uterine arteries and in umbilical artery and the fetal vessels, if indicated. Immediately after dialysis, uterine contraction monitoring and pharmacologic tocolysis.	
Barua *et al.* (5), 2008	HD	Not specified	Antenatal care by an obstetrician specialized in high-risk pregnancy working closely with a designated nephrologist.	Biochemical tests at least monthly
Tan *et al.* (16), 2006	HD and PD (1 case)	Not specified	Antenatal visits (at least every 2 wk) by obstetricians and renal physicians. Intensive fetal monitoring, serial fetal biometric measurements, biophysical profile, fetal Doppler velocimetric assessment. Decisions regarding mode and timing of delivery based on standard obstetric indications. On dialysis check for dialysis-induced contractions.	Monitoring of fluid status, BP, maternal weight, biochemical test, and adequacy of dialysis. Targets: BP 140/90 mmHg, pH and electrolytes at near normal, urea <20 mmol/L
Malik *et al.* (8), 2005	HD	Not specified	Obstetric evaluation every 2 wk.	
Haase *et al.* (17), 2005	HDF	Not specified	Patients followed by department of gynecology and obstetrics. First ultrasound, before and after dialysis, immediately after diagnosis of pregnancy. Fetal ultrasonography every 10 d or more frequently. Measurements of fetal biometry; estimated fetal weight; Doppler velocity of uterine umbilical and medial cerebral arteries; signs of fetal stress; hydramnios and cervical length. CTG up to daily after the 25th week	High-protein diet (<100 g of protein, 3000 kcal/d). No dietary or fluid restrictions. Targets: hematologic and metabolic parameters to near physiologic levels. Kt/V double-pool repeatedly calculated
Eroğlu *et al.* (7), 2004	HD	Not specified	Patients followed in collaboration by obstetrician and nephrologist. Monitoring by ultrasonography every 2 to 4 wk. Monitoring of fetal well-being after 24 wk, including cardiotocography twice weekly and weekly Doppler flow measurements. Immediately after dialysis, uterine contraction monitoring.	
Moranne *et al.* (18,29), 2004	HD	Not specified	Not specified (letter)	
Luciani *et al.* (19), 2002	HD	Not specified	Follow-up by nephrologist and obstetrician. Obstetric surveillance: fetal heart rate monitoring immediately after dialysis. Ultrasonography every 2 wk for control of fetal growth.	Careful measuring of maternal BP daily
Chao *et al.* (12), 2002	HD	Followed by pediatrician for 1 yr	Not specified (retrospective analysis of clinical charts)	Counseling on changes in dialysis treatment, prenatal surveillance, and risks of the pregnancy

HD, hemodialysis; HDF, hemodiafiltration; PD, peritoneal dialysis; CTG, cardiotocography.

Table 3. Dialysis regimen and therapy

Reference	Type of Dialysis	Dialysis Duration	Dialysate
Chou *et al.* (9), 2008	HD and PD	Overall 15 to 27 h/wk; on PD dialysis, volume decreased with the enlargement of the uterus	Flow 500 ml/min; dialysate changed on basis of results of blood tests
Bamberg *et al.* (15), 2007	HD	As much dialysis as tolerated, at least 24 h/wk	Flow 500 ml/min; because of intensified dialysis, dialysate was modified
Barua *et al.* (5), 2008	HD	Frequency 5 to 7 nights/wk; duration 8 h	Flow 500 to 750 ml/min; sodium 137 to 140 mEq/L, potassium 1.5 to 2.0 mEq/L, bicarbonate 35 mEq/L, calcium 6 to 7 mg/dl
Tan *et al.* (16), 2006	HD and PD (1 case)	HD frequency 6 times/wk; duration approximately 3 h; target urea <20 mmol/L	Not specified
Malik *et al.* (8), 2005	HD	Frequency 4 to 6 times/wk; target BUN <18 mmol/L	Bicarbonate buffer
Haase *et al.* (17), 2005	HDF	As much as tolerated, at least 24 h/wk	Flow 500 ml/min; bicarbonate 28 mmol/L, sodium 138 mmol/L, potassium 3.0 mmol/L, calcium 1.25 mmol/L, chloride 110 mmol/L, magnesium 0.5 mmol/L
Eroğlu *et al.* (7), 2004	HD	Frequency 4 to 6 times/wk; duration 4 h; target BUN <60 mg/dl and creatinine <6 mg/dl	High calcium and bicarbonate bath
Moranne *et al.* (18,29), 2004	HD	Systematic increase of session number and time	Not reported (letter)
Luciani *et al.* (19), 2002	HD	Length and frequency determined according to predialysis values	Calcium 1.75 mEq/L, sodium and potassium upon needs
Chao *et al.* (12), 2002	HD	During pregnancy, hemodialysis schedule was increased to 4 h per dialysis session and 4 to 6 times/wk	Blood flow 250 to 300 ml/min; dialysate 500 to 600 ml/min; high calcium and bicarbonate bath

BUN, blood urea nitrogen; EPO, erythropoietin; Hb, hemoglobin.

Despite the great theoretical interest in this issue, preconceptional counseling is rarely a part of the clinical workup for the female patient on dialysis (11,12). According to a small, informal survey performed in our limited care home dialysis center in 2003 (on the occasion of an unwanted pregnancy in one of our young patients [13]), none of the 18 women who were of childbearing age and on dialysis treatment at that time ever thought of the possibility of becoming pregnant while on dialysis or considered the possibility of planning a pregnancy before transplantation. The aim of the study was to review systematically the recent literature (2000 through 2008) on pregnancy during dialysis, with particular attention to the setting of study and to the dialysis schedules and control policies as the basis for evidence-based counseling for young patients who are on long-term dialysis.

Materials and Methods

Search Strategy

The first search strategy was built on Medline on OVID (November 2008, first week), on chronic kidney disease (CKD) in pregnancy. The search was deliberately broad to increase sensitivity, according to the guidelines of the Cochrane Collaboration (14). Terms used as MESH (preindexed on Medline) or free terms (combined with *or*) were the following: Pregnancy as MESH and free term, and additional MESH terms were pregnancy complications, pregnancy tests, pregnancy trimester, pregnancy rate, pregnancy in diabetics, pregnancy proteins, pregnancy, pregnancy outcome, pregnancy maintenance, and pregnancy high-risk; nephropathy and renal diseases as MESH and free term, and additional terms were renal dialysis, chronic kidney failure, hypertension, kidney diseases, systemic lupus erythematosus, glomerulonephritis, nephropathy, polycystic, and CKD. Peritoneal dialysis was included in "dialysis." The following limits (as provided by Medline) were used: human, English, and period of publication. An additional search was performed in duplicate (working independently and matching results) by A.C. and G.B.P., using MESH and free terms on pregnancy and dialysis, including also hemodial$ haemodial$, hemofiltr$ haemofiltr$, and hemodiafiltr$ or haemodiafiltr$; the same limits were added. Review studies were retrieved to allow screening for references that might have escaped previous searches. An additional manual search was also carried out, controlling the reference lists of the reviews, selected articles, and textbooks. Patients with CKD and transplant patients were not considered. To reduce publication bias, we did not include single case reports on dialysis and we retrieved only articles that reported on at least five cases. The abstracts and titles were screened by A.C. and G.B.P., and controversies were resolved by discussion. The final selection of the articles was agreed on, and the data were extracted in duplicate, according to the Cochrane method (14).

Table 3. Continued

Dialyzer/Blood Flow	EPO, Iron, and Vitamins (Anticoagulation)	Other Drugs as Reported in Articles	Weight Gain/Other
High-flux dialyzer; blood flow 200 to 300 ml/min	Blood transfusion, EPO, and oral iron supplementation	Hydralazine, nifedipine	Volume-controlled dialysis sessions
Biocompatible nonreuse high-flux dialyzer	EPO and iron intravenously; in case of severe anemia, blood transfusions; trace elements, vitamins D, B_{12}, B complex, and folate	Fenotorol, magnesium for uterine contraction, celestan in preterm delivery	Maternal weight increased by 500 g every 10 d if appropriate
F80 polysulfone dialyzers or Exceltra 120 dialyzers; blood flow 300 to 400 ml/min	EPO, intravenous iron	α-methyldopa, labetalol, phosphate	Not specified
Not specified	Increase of EPO, water-soluble vitamins, folate	Methyldopa, hydralazine, labetalol, low-dosage aspirin	Positioning to avoid supine hypotension
High-efficiency biocompatible membranes	EPO adjusted to target Hb >10 g/dl; heparin bolus 1000 IU followed by 250 IU/h	Not specified	Slow-rate ultrafiltration
Biocompatible nonreusable high-flux dialyzers with surface area of 1.7 m^2; blood flow gradually increased during the first 15 min of HDF to the highest tolerated	EPO beta adjusted to target hematocrit >35%; intravenous iron to transferrin saturation 30 to 50%; trace elements, vitamin B_{12} and folate intravenously to keep values within normal range; unfractionated heparin	Tocolysis: β-mimetics, magnesium	Maternal weight increased by 200 to 400 g every 10 d if appropriate
High-flux dialyzer; blood flow 200 to 250 ml/min	EPO 1500 to 3000 U 3 times/wk; target Hb >9 g/dl	α-methyldopa, hydralazine	Weekly weight gain ≤300 g during the second trimester; 300 to 350 g/wk during the third trimester
Not reported (letter)	Not reported (letter)	Not reported (letter)	Not reported (letter)
High-efficiency or high-flux dialyzer	EPO as usual, iron and folates; continuous heparin without a loading dose	Not specified	Maternal weight gain estimated according to estimated fetal weight
High-flux dialyzer; a conventional dialyzer used for additional dialysis	Anticoagulation with heparin altered only when delivery was imminent	Not specified	Dry weight gradually increased, depending on obstetric status

Data Analysis

The following data were extracted: Title, author, objective, year, journal, period of study, multicentric, country, type of study, number of cases, maternal age, type of disease, known/new diagnosis, subcategories, para, hypertension, preeclampsia, proteinuria, other complications during pregnancy, drugs, additional care, gestational age, birth weight, indication to delivery, induction, mode of delivery, preterm delivery, other maternal complications (short and long term), stillbirth/neonatal death, small for gestational age (SGA), admission to intensive care unit, other neonatal complications (short and long term), and maternal and fetal follow-up. All available data on dialysis schedules and renal support therapy were also gathered.

The decision to perform a narrative or a meta-analytical systematic review was subordinated to the analysis of the type and quality of evidence retrieved. Because we were expecting to deal with a low number of cases and high heterogeneity, a descriptive narrative review was planned.

Results

Retrieving the Evidence and Summary Data

In our first search on CKD and pregnancy, 241 full-text articles were retrieved from 2840 references; four fulfilled the selection criteria, five articles were added from the additional search, and one letter was found in reference lists (overall nine full articles and one letter). The overall data are summarized in Table 1. The 10 studies include 90 pregnancies in 82 patients. All but one of the studies were monocentric. Because case reports were not included, the number of observed patients ranged from five to 15. One study was from North America, four were from Europe, three were from Asia, one was from Turkey, and one was from Saudi Arabia. The studies were heterogeneous for duration (from 2 to 16 yr) and period of study (1988 through 1998 to 2000 through 2006) and median or mean age of the patients (25 to 35 yr; Table 1). The specific causes of end-stage renal failure were reported in five of 10 studies; the letter referred to a full article for details (missed in the search because of the non–English language publication [18]); however, the definitions were heterogeneous, and some of them may be questionable (*e.g.*, acute glomerulonephritis or preeclampsia) or were probably more correctly labeled as comorbidities (ischemic heart disease or parathyroid adenoma; note to Table 1). All but one of the studies (the letter, which referred to the full article published in French) supplied information on support therapy (Table 2); however, support therapy and obstetric control policy were heterogeneous, as were the drugs specifically mentioned in the articles. Some studies gave

Table 4. Maternal and fetal outcomes

Reference	Gestational Age (wk)	Birth Weight (g)/IUGR	Indication for Delivery	Cesarean/Induction
Chou *et al.* (9), 2008	HD group: 30.8 ± 1.6	HD group 1511 ± 284; IUGR 28.5%	Only for cesareans: previous cesareans	HD 43% to NR
Bamberg *et al.* (15), 2007	32 (30 to 37)	1764 (1274 to 2465); IUGR 80%	Pathological Doppler, fetal distress, elective	80 to 20%
Barua *et al.* (5), 2008	36.2 ± 3.0	2417.5 ± 657.0; IUGR 17%	IUGR, failure to progress and nonreassuring fetal heart rate, multiple comorbid conditions	33 to 17%
Tan *et al.* (16), 2006	31 (26 to 36)	1390.0 ± 705.3; IUGR 27.3%	HELLP, obstetric cholestasis, abruptio placentae, IUGR + hypertension, PE	55.6% to NR
Malik *et al.* (8), 2005	31.5 (27.0 to 36.0)	1700 (1115 to 2300); IUGR 70%[b]	NR	33 to 0%
Haase *et al.* (17), 2005	32.8 ± 3.3	1765 ± 554	Fetal distress	80 to 0%
Eroğlu *et al.* (7), 2004	32 (26 to 36)	1400 (420 to 2640); IUGR 14%	IUGR, PE, PROM, preterm labor	57 to 14%
Moranne *et al.* (18,29), 2004	31 (24 to 34)	1495	NR	NR
Luciani *et al.* (19), 2002	28.6 ± 4.0	1431 ± 738	Abruptio placentae, fetal distress, PROM	80% to NR
Chao *et al.* (12), 2002	32 (23 to 36)	1542 (512 to 2660); IUGR 80%	Fetal distress, previous cesarean section, breech, placenta previa, preterm labor, PROM	46 to 7%

CPAP, continuous positive airway pressure; HELLP, hemolysis, elevated liver enzymes, and low platelet count; IUGR, intrauterine growth restriction; NICU, neonatal intensive care unit; NR, not reported; PROM, premature rupture of membranes; RDS, respiratory distress syndrome.

[a]Excluding two abortions that occurred at 9 and 20 wk.

[b]Excluding perinatal mortality.

[c]Excluding spontaneous abortions and perinatal mortality.

detailed definitions of the diet and the control policies of mother and fetus, whereas others merely mentioned a close interaction among physicians (nephrologists and obstetricians).

Dialysis Schedules

All studies reported dialysis schedules (Table 3). Daily dialysis or schedules more frequent than the conventional three times per week were the most common, but type of treatment, membranes, and blood flows varied. Five studies reported the dialysate flow rate (range 500 ml/min to 500 to 750 ml/min), and one study (8) reported using slow-rate ultrafiltration. Total dialysis time per week differed among the studies, and an exact amount of time was seldom given, in keeping with a widespread flexibility of dialysis policies and a widespread attitude toward tailoring dialysis regimens. Two studies (9,17) gave the indications "as much as patient could take" and "at least 24 h/wk." Three studies did not report on the duration of a dialysis session, so it is impossible to determine the minimum amount of dialysis per week. For the studies that did provide this information, the lowest minimum was 15 h (9) and the highest minimum was 40 h (5) (Table 3). This all underlines that dialysis schedules may change over the duration of pregnancy, and it may be difficult to standardize them fully.

Reports of medications were also not comparable. Erythropoietin was mentioned in seven of the dialysis regimens (Table 3). Only one gave an indication of the amount used, saying that the physicians administered "1500 to 3000 units three times per week" (7). The target hemoglobin was cited by two studies only, which used different targets (≥9 and ≥10 g/dl, respectively). Vitamin supplementation was mentioned in most articles (Table 3).

Outcomes: The Mother

Hypertension and anemia were the most frequent clinical concerns on the mother's side (Table 4). Anemia was indirectly a common complication; the increase in the use of recombinant erythropoietin and the need for blood transfusions was cited in the sections on intradialytic management in most articles (Table 3). Dialysis-related hypotension was cited in some articles as a

Table 4. Continued

Preterm Delivery	Stillbirth/Neonatal Death	Admission to NICU	Maternal Hypertension	Other
HD 71%; PD 67%	HD 28.5 to 14.0%; PD 33 to 33% (3 stillbirths, 2 deaths)	NR	HD 57%	Three pregnancies were terminated in the first trimester (elective abortion); polyhydramnios: HD 71%, PD 33%
80%	None	100% (mean 17 d range 3 to 50 d)	Severe hypertension 20%	Polyhydramnios 40%; cervical shortening 60%, RDS 20%, mild respiratory dysfunction 40%, hyperbilirubinemia 60%; 1 patient developed anuria
NR	None	33% (1 to 7 d)	Two patients required medication for hypertension 33%	One elective abortion; shortened cervix at 25 wk 17%, vaginal spotting 17%, SGA 17%; neonatal jaundice 17%; Apgar: 9/9, 5/8, 9/9, 6/9, 8/9, 5/7
100%[a]	None	55.6%	HD 63%; PD 60%	Two intrauterine deaths <22 wk (spontaneous abortions); polyhydramnios 18%, low birth weight 77.8%, abruptio placentae 1, acute pulmonary edema 1, PROM 2, obstetric cholestasis 2, hemorrhage 1, venous thromboembolism 2, peritonitis 1, Apert syndrome 1
100%[c]	17% (2 perinatal deaths)	NR	66% preeclampsia	Three spontaneous abortions; hydramnios 42%, oligohydramnios 8%, rupture of uterus 1
80%	None	Days in NICU: 13, 3, 13, 4, 50	Severe hypertension 40%	Mild polyhydramnios 40%, oligohydramnios 20%, cervix insufficiency 60%, hypermagnesemia 20%; mean maternal hospital stay 85 ± 61 d; RDS requiring CPAP 80%, length of NICU stay 26 ± 18 d, all discharged healthy
100%	0 to 14% (1 neonatal death)	NR	29% preeclampsia	Polyhydramnios 29%, PROM 29%, RDS 14%; Apgar ranged from 2/8 to 4/10
NR	20% (1 neonatal death)	NR	NR	One elective abortion
100%	20% (1 stillbirth); 1 death at 9 mo, 1 at 5 yr	NR	One case of gestational hypertension	Polyhydramnios 5/5, vaginal infections 5/5, RDS 40%, congenital anomalies 20%; Apgar 0/6, 8/9, 0/4, 7/8
100%	8% (1 stillbirth) to 23% (3 neonatal deaths)	NR	Severe hypertension in 7 patients	Five elective abortions; Polyhydramnios 6/13, oligohydramnios 2/13, PROM 4/3, premature contraction 7/13; Apgar: 8/10, 7/8, 2/4, 1/3, 5/9, 4/7, 9/10, 9/10, 3/6, 9/10, 8/10

complication of the dialysis session. No article gave information on the magnitude of the residual renal function, if and when present. The definition of hypertension was given in two studies only and was different in both of them: The first one referred to a systolic pressure taken twice 6 h apart of >140 mmHg or diastolic BP of >100 mmHg after 20 wk gestation, whereas the second set the level of two BP readings at least 4 h apart at >140/90 mmHg (9,16). A third study defined severe hypertension as BP >160/110 mmHg (7). The definition of preeclampsia was given in one study only, which was any worsening of hypertension during the second half of pregnancy (8).

Outcomes: The Offspring

Intrauterine deaths and preterm infants were the most commonly reported complications. The reporting of outcomes was far from homogeneous (eight of 10 studies reported on preterm delivery, and one of 10 studies reported on SGA; Table 4).

In only one article (8) was preterm delivery defined as birth before 37 wk; the other authors did not specify the week used as cut point for preterm delivery. However defined, the incidence of preterm delivery as reported in the articles was extremely high: The lowest reported percentage was 67%, and the percentage was 100% in five of eight studies that reported data on this topic. Moreover, the authors usually did not specify the real causes of preterm delivery, whether attributable to iatrogenic causes (fetal-maternal pathology) or to spontaneous labor. Similar methodologic concerns apply to intrauterine growth restriction, the definition of which was given in only one article (9).

Polyhydramnios was reported as a complication in eight studies, with an incidence ranging from 18 to 100% of the cases; however, the same lack of definition applies to (poly)hydramnios, because it was defined in only two studies, once again with different cutoffs: Amniotic fluid index of >25 cm measured by sonography and amniotic fluid index >22 (9,15).

Respiratory distress syndrome was reported as a complication in four studies, the prevalence ranging from 14 to 80%. The incidence of spontaneous abortions was reported in two of the 10 articles (Table 4).

Within these limits, the overall possibility of a pregnancy's resulting in a live offspring ranged from 50 to 100% (Table 4). When the data on the pregnancies were summarized (with all of the limits of pooling heterogeneous data), there were 10 elective abortions, five spontaneous abortions, and 14 stillbirths/neonatal deaths of 90 conceptions in 78 patients. Two other infants were reported to have died at 9 mo and 5 yr (19). Excluding these two infants because long-term data were not available in the other articles, this results in 61 (81.33%) surviving infants of 75 pregnancies or, when spontaneous abortions are considered, in 61 (76.25%) surviving infants of 80 pregnancies.

Discussion

Pregnancy is a challenge for women with kidney disease, and this is especially true for dialysis patients (20); however, the impressive improvement in maternal–fetal care and the continuous improvement in dialysis efficiency, frequency, and support therapy allows them to reach previously inaccessible targets (20–23). In view of the many social changes in a globalized society, we conducted this systematic review to try to answer the question of whether it is time to reconsider our present counseling policy regarding pregnancy for women who have ESRD and are on dialysis, and, if so, the evidence-based information that we are able to supply. Our systematic search retrieved relatively few articles, particularly with respect to a much larger number of reports on CKD in the pre-ESRD phase and on kidney transplant women (23). This suggests that report biases are to be expected and that, in accordance with the characteristics of publication biases, the data published so far may reflect particularly fortunate series from experienced centers. Within these limits, the results of 90 pregnancies reported in the new millennium (even if from different periods [Table 1] and excluding single case reports) confirm that pregnancy is still a challenge but also a possibility (Tables 1 through 4).

The high heterogeneity of the cases, of the dialysis schedules, and of the settings and periods of observation does not allow a fully reliable pooling of the data; however, as a rough reference figure obtained by pooling the pregnancies that resulted from 90 conceptions in 78 dialysis patients, we can say that there were 61 surviving infants of 80 pregnancies, excluding 10 elective abortions (76.25%), or 61 surviving infants of 75 pregnancies when the five spontaneous abortions were excluded (81.33%; Table 4). In light of the heterogeneity of the data, any attempt to correlate outcomes with dialysis therapy is hazardous; however, that the best results are reported in settings of long daily dialysis suggests that dialysis efficiency plays an important role. More in detail, the three series that were free of neonatal death and stillbirth are those that used the longest and most intensive treatments (long nightly dialysis and "as much dialysis as the patients could tolerate") (5,15,17). These account for 15 of 15 live infants of 16 conceptions (one elective termination), which is a favorable outcome in comparison with the 46 of 60 live infants with the other dialysis schedules, although the difference does not reach statistical significance ($P = 0.059$). Of note, the suggestion of a central role for a high dialysis dosage allows an explanation for an overall improvement of the results recorded in the past decade, when increased dialysis time and frequency became a systematic tool for following pregnancies in dialysis (11).

Although it is very hard at present to draw clear conclusions, the increasing number of patients who are able to go throughout pregnancy all over the world should prompt us to include the issue of counseling in the usual care of dialysis patients. Only expert opinions that are based on a limited number of data are presently possible. Within these limits, we suggest that counseling touch on the following points: Success rate, risks to the mother, demands on the daily life of the pregnant patient, and long-term results.

The women should be informed that the success rate (broadly defined as the birth of a live baby, without major clinical problems at birth) is growing and is approaching 75%. In the series selected for our review, two malformations were recorded, in line with the risk in the overall population (Table 4). The risk for death of the mother seems very low, and no case was recorded in the series considered; however, morbidity is high, and, even if specific data on hospitalizations are not reported, the long list of complications suggests a likelihood of long hospitalizations (Table 4).

Pregnancy on dialysis is very demanding, and a woman has to be prepared to undergo dialysis as much as possible, up to 8 h per night, taking into account that the best results were obtained in settings of long nightly dialysis or of "as much dialysis as the patient would tolerate." Overall, we suggest stressing that the switch to daily dialysis is probably one of the main reasons for the improvements in outcomes observed in the past decade.

As for the short-term results, a crucial issue regards preterm birth (approximately 70% to 100%) and the risk for a SGA or low birth weight infant (up to 100% of the cases). Although the long-term risks for "small children" are still matter of discussion and long-term sequelae cannot be excluded, the need for a long stay in the neonatal intensive care unit also has to be taken into account.

Overall, we believe that the patient should be advised that long-term experience on the potential diseases in the offspring is lacking, because the numbers are small and the follow-up is scattered and still short. There are some data on a higher risk for cardiovascular diseases in small infants (or in SGA infants), but the confusion on low birth weight, SGA, and intrauterine growth restriction adds to the general uncertainties, and the generalization to dialysis patients of findings that are emerging in the overall population may be hazardous (24–28).

Discussion of birth control is beyond the scope of this review; however, because most of the pregnancies reported were unplanned, we suggest taking into account birth control policy at counseling. In this field, too, there is no robust evidence leading to preference of one method over the others. In addition to the problems commonly encountered in the overall population, such as low reliability and low cul-

tural acceptance of the barrier methods, intrauterine devices have the disadvantage of infectious risks, which are believed to be higher in dialysis patients, and hormonal contraception should be banned for patients with active immunologic diseases. Once more, a tailored approach is crucial in this delicate patient population.

It is likely that only an international registry of pregnancies in dialysis patients will help us to answer the many open questions on the best treatment and on the actual results. Further important clues, presently not covered by the literature retrieved, will regard the quality of life, the psychological impact of medical care and frequency/duration of dialysis, and the burden of hospitalizations for the patient as well as for the health care system. While awaiting a large-scale international collaboration, we should advise patients on the limits of the present knowledge and that, although the first report of a successful pregnancy in dialysis dates to 1971, treating a pregnant woman who is on dialysis is still based on sporadic and, to some extent, experimental experiences (1,11).

Conclusions

Evidence on pregnancy in dialysis patients is scattered and heterogeneous. The growing number of reports from all over the world convey the message that pregnancy, even if at high risk, should not be automatically discouraged in dialysis patients. These observations suggest that we should reconsider our routine counseling policy, which only rarely includes the issue of pregnancy in young dialysis patients.

Disclosures

None.

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