

Dialysis and Pregnancy-A Review

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Abstract

Pregnancy in the End Stage Renal Disease (ESRD) population is one of the most complex clinical challenges for healthcare providers. Current guidelines, peer-reviewed publications, and textbook chapters were utilized in this review to determine the best practices for dialysis during pregnancy, extending to immediate post-partum period. The purpose of this review is to impart healthcare providers with current practice recommendations for the best health outcomes for the mother and fetus.

Introduction

Pregnancy in the dialysis population is one of the most complex clinical challenges for healthcare providers. Pregnancy causes significant changes in the body, including increases in blood volume, resistance to vasoconstrictors, urine protein excretion, cardiac output, and rise in Glomerular Filtration Rate (GFR) by approximately 50% [1]. It also leads to a decrease in serum creatinine level, blood pressure and vascular resistance [1]. Majority of individuals with End-Stage Renal Disease (ESRD) or renal failure being managed by dialysis have complex health concerns associated with this condition. ESRD complicates every step of the process of having a biological child by natural conception. Continuing a pregnancy to successful full-term delivery is challenging in individuals of childbearing age with ESRD and there is increased risk of morbidity and mortality for both the mother and fetus.

Healthcare providers caring for this population must have access to evidence-based practice research that guides their current practice indicates future trends and decreases risk to this population. PubMed search on the topics of “dialysis and pregnancy” and “pregnancy in renal disease” yields a multitude of publications on this complex clinical situation. With the abundance of information available, providers especially in the areas of obstetrics/gynecology and nephrology need clear, up to date recommendations to provide day to day management of this population. The purpose of this review is to impart healthcare providers with current practice expectations and recommendations for the best health outcomes for the mother and fetus.

Method

Two trainees conducted independent literature review under faculty supervision with the aim to understand current practice expectations. Current guidelines, peer-reviewed publications on

PubMed, and textbook chapters were utilized in this narrative review to determine the best practices for dialysis during pregnancy. The databases used were PubMed, goggle, nephrology textbooks and practice guidelines, Search terms used were “Pregnancy and dialysis” which resulted in over 2000 articles. Further filters were used to select articles ‘human’ and published in the last 5 years. However, we individually looked up older articles for some data on hormones and historically relevant data as we wanted to present some background to the current understanding without overwhelming details. This resulted in screening 250 articles. We then reviewed these articles and picked the ones cited here based on the focus of this review, which was to focus entirely on the pregnant dialysis population practice expectation development.

Incidence and outcomes data

Women with ESRD on dialysis have increased difficulty with conception due to significant abnormalities in hormones consequent to renal failure [2]. The majority of these women continue to be discouraged at conception and maintaining pregnancy. However, with improved outcomes on Hemodialysis (HD) and Peritoneal Dialysis (PD), as well as increasing renal transplant rates, the incidence of pregnancy in this population does show a continued rise [3,4]. The US live birth rates which were noted to be less than 40% in the 1980s have now shown an increase to approximately 80% over the last several years [2,4,5]. Review of the literature reveals that since the first reported case of a successful outcome on dialysis in 1971 [6,7] there is now significant data on reported cases of pregnancy in women receiving HD [2,4,5].

A comparison of women on dialysis HD and PD in US and Germany exhibit successful outcomes in 40% and 50% of these respective populations [2]. Recent data on pregnancy in women on dialysis describes the median gestational age of neonate as 33.8 weeks

with a median birth weight of 1750 grams [8]. Greater than 40% of these pregnancies extend over 34 weeks; prematurity of less than 28 weeks is noted as 11.4% and 28-day neonatal survival rate of 98% [8,9]. As expected, better outcomes with respect to conception and pregnancy are noted in ESRD individuals that have a residual renal function reemphasizing the need to preserve residual function in the ESRD population [8]. Best opportunity for conception is within 2 years of initiation of dialysis as chances of conception decreases with time on dialysis [10].

Symptoms and complications of ESRD, such as anemia, enhance other complications including hypogonadism, lower libido, and poor self-image [11]. Data suggest that approximately 84% of women with ESRD reported sexual dysfunction and only 35% of women reported being sexually active. Hormonal imbalances result in anovulatory cycles [12]. In addition, maintaining a pregnancy to near term can be difficult. Higher incidence of lost pregnancies, intrauterine growth restrictions, placental detachment, anemia, infections, premature rupture of membranes, polyhydramnios, uncontrolled hypertension, preeclampsia, eclampsia, hemorrhage, cesarean sections, small for dates neonates and premature labor, pre-term birth followed by postpartum conditions continue to be challenges faced by most women on dialysis [2,6].

Pregnancy is considered harder to achieve on Peritoneal Dialysis (PD) due to concerns regarding a possible barrier of PD fluid to normal ovum migration. About 1.1% of reproductive age women on PD conceived *versus* 2.4% on Hemodialysis (HD) [13]. Regardless, the outcomes of pregnancy are similar as PD provides an opportunity for high-efficiency dialysis.

Diagnosis and maintenance of pregnancy

Most individuals suffering from ESRD have hormonal imbalances leading to complexities in the diagnosis and maintenance of pregnancy. Ultrasound examinations are considered to be ideal to diagnose pregnancy and also to assess fetal well-being [2].

Common symptoms associated with ESRD include amenorrhea, nausea, and vomiting. Lab values demonstrating anemia and increased HCG levels are usual with or without pregnancy. Pregnancy-associated plasma protein-A levels are higher in patients on HD and levels are increased by the administration of heparin [13-16]. These abnormal lab results raise concerns about false-positive pregnancy screenings and Down's syndrome screening.

As Chronic Kidney Disease (CKD) progresses, there is a release of Gonadotropin-Releasing Hormone (GnRH) regulating the basal secretion of the gonadotropins. Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) appear to remain normal, but there is a loss of the normal cyclic release of GnRH by the hypothalamus, leading to loss of normal pulsatile gonadotropin secretion by the pituitary and resulting in impaired ovulation. The definitive cause for this is unknown but increased amounts of prolactin, GnRH and LH caused by reduced renal clearance have been implicated [17,18].

Treatment with PD or conventional HD does not restore this function; however, treatment with increased intensity of HD [2] and kidney transplantation [19] often, but not always, restore menses and fertility (Table 1).

Hemodialysis for pregnancy maintenance

The most common dialysis modality for the general population is HD. Most pregnant ESRD patients also tend to fall under this modality, which is second only to renal transplant. HD offers benefits of in-

center care, intensification of dialysis as needed and time flexibility. Home HD would be an optimal choice for many of these patients as it also offers maximum benefits of dialysis without compromising independence.

The dialyzer recommendations have been to use highly biocompatible and no re-use filters. Earlier, low flux was recommended to prevent rapid osmolarity and fluid changes. In recent practice, targeting low ultrafiltration allows for high flux membrane use for better clearance of middle molecules, without causing rapid changes. Due to increased time on dialysis, middle molecule clearance is not a major concern and we would recommend facility preferred flux dialyzer for cost prudence.

More intensive dialysis schedule is preferred targeting average blood urea nitrogen levels <16-18 mmol/L. This is usually achieved by increasing the frequency of HD to 5-7 times per week, or switching to long nightly HD, targeting a weekly clearance (Kt/V) of 6-8. Usually, between 37-56 hours of dialysis per week is optimal [3,5,6, 12,14,17-20].

A recent study has indicated lower values to be effective with an overall successful delivery rate at 89.2%, with a dialysis regimen of 2.6 ± 0.7 h/d, 15.4 ± 4.0 h/wk and mean weekly standard urea Kt/V of 3.3 ± 0.6 [21]. Available data validate the use of intensive hemodialysis as a standard in care for pregnant women with ESRD. The literature review discusses a comparison of live birth rates based on dialysis time. In a study, one group received approximately 20 hours dialysis per week while the comparison group received high-intensity dialysis nearing 35-40 hours per week. Targeting approximately 35-40 hours dialysis conveyed approximately 30% increase in the live birth rate [15]. Intensive dialysis is highly recommended as this reduces uremia and adverse effects on the fetus. Intensive dialysis may also be achieved by a combination of PD and HD, including long treatment time on night cycler, increase in fluid volume as tolerated. However, as the pregnancy progresses, there will likely be a need to decrease volume and instead focus on increasing exchanges [22] (Table 2).

Anticoagulation

Anticoagulation is a routine practice on HD as it prevents significant clotting of blood in the lines during dialysis treatments. Clotting of lines with the inability to return blood in the line to the patient is one factor that can impact anemia in this population. We advise the use of a minimum required dose of heparin. It is not considered to be harmful as it does not cross the placenta. There is no available data on newer anticoagulants so use in this population is not recommended.

Aspirin can be used for preeclampsia prophylaxis but needs to be stopped in the last few weeks of pregnancy in anticipation of delivery [2,19,23].

Peritoneal dialysis

Intensifying Peritoneal Dialysis (PD), as the pregnancy progresses, by decreasing volumes and increasing the number of cycles is sufficient for most patients. Supplemental HD can also be utilized if necessary. Some patients can attempt combination therapies with both modalities. Icodextrin can be utilized when benefits outweigh risks, though it remains a category C drug [24,25].

Dry weight management

Dry weight management is a challenge in most hemodialysis patients. The complexity increases when pregnancy weight gain must be factored into this equation. Ultrafiltration goals need to be relaxed to accommodate for the weight gain of pregnancy. However, a close

Table 1: An overview of pregnancy related hormones in dialysis [9].

Hormone	Normal secretion in pregnancy	Status on HD	Status on PD	Function
Human Chorionic Gonadotropin (HCG)	Elevated with pregnancy	Elevated with dialysis	Elevated with dialysis	Development of anchoring villi during pregnancy (establishment and maintenance of pregnancy)
Thyroid Stimulating Hormone (TSH)	Elevated T3, T4, result in lower TSH values	10% increase or decrease both have been reported	Despite large TBG losses, no major change noted, however early thyroid failure has been noted in non-pregnant PD pts warranting follow up	Increased FT ₃ ,T ₄ to maintain increased metabolic demands of pregnancy
Prolactin	Anterior pituitary hormone, increases throughout pregnancy	ND	ND	Increases during pregnancy to lactation
Progesterone	Up to 10 weeks secreted from the corpus luteum, then by placenta	ND Average change reported about 15%, not considered to be clinically significant.	ND	Prepares endometrium, required for implantation, suppresses maternal rejection of trophoblast, prevents preterm labor Postpartum fall was not noted in one case report [8,9]
Human placental lactogen	Produced and secreted by the syncytiotrophoblast of the placenta	ND	Data unavailable Considered ND	Promotes fetal growth
Follicle Stimulating Hormone (FSH)	Together with LH, the gonadotropins stimulate ovarian follicle and help further the pregnancy cascade hormones	Data unavailable Considered ND	Data unavailable Considered ND	Maturation of primordial cells
Luteinizing Hormone (LH)		Data unavailable Considered ND	Data unavailable Considered ND	
Estradiol		Gradual suppression	Gradual suppression	Promote uterine blood flow, myometrial growth, stimulate breast growth
Adrenocorticotrophic hormone (ACTH)		ND, but a significant increase is noted after dialysis likely due to stress of dialysis	Not as high as HD	
Oxytocin	Post Pituitary hormone, concentrations rise continuously till parturition			Parturition and the “let down” response during lactation
Antidiuretic hormone (ADH)	Post pituitary, the metabolic clearance rate of ADH increases in the second trimester due to vasopressinase released by the placenta			

ND- Non-dialyzable; PD-Peritoneal dialysis; HD-Hemodialysis

Table 2: Example of an optimal HD prescription in Pregnancy.

Datapoint	Optimal
Blood flow	400-450 ml/min
Dialysate flow	500-800 ml/min (1.5-2 times blood flow)
Sodium	135-145 mEq/L
Potassium	4 K bath mEq/L
HCO ₃	25 mEq/L (lowest)
Calcium	2.5-3 mEq/L
Ultrafiltration	As tolerated (make allowance for weight gain, low targets)
Time	5-6 hours per treatment (40 hours a week)
Dialyzer	Biocompatible(facility preferred)

watch on blood pressure and physical signs and symptoms must be kept, as these patients are at risk of rapid fluid overload. About 1 kg gain in weight is expected in the first trimester, followed by about 0.5 kg per week in 2nd and 3rd trimesters. Avoiding large volumes of fluid removal or ultrafiltration is of paramount importance to prevent compromised uterine blood flow. Calculation of total intake and output with daily patient logs assists in the assessment and management of weight [6,22,23,26]. In the authors' experience, pregnant ESRD patients are quite well informed and diligent regarding keeping logs as needed, especially as they are aware of the high-risk pregnancy state.

Anemia

Anemia is common in both pregnancy and ESRD. This is compounded with HD. PD offers some advantage as there is no loss of blood. The use of Erythropoiesis-Stimulating Agents (ESA) (pregnancy category C) to treat anemia is generally required. There are case reports of the use of darbepoetin with success in pregnancy, with no obvious unexpected side effects. ESA dosing may need to be (two to three-fold) higher in these patients. Vitamin B12 and folate replenishments are recommended. If iron deficient, intravenous iron sucrose (pregnancy category B) can be used [4].

Target hemoglobin of 10-11 g/dL is ideal.

Bone mineral disease management

Sevelamer, lanthanum, aluminum, cinacalcet, and paricalcitol have not been well tested or established for use during pregnancy. Intensification of dialysis should prevent the need for these medications and allow for stable electrolyte levels. There are case reports of successful outcomes with cinacalcet, however, more data is needed prior to making recommendations regarding the administration of this medication [27].

Phosphorus and vitamins (vitamin C, thiamine, riboflavin, niacin, B6) may need to be replenished as these are removed in dialysis.

Elevated phosphorus can safely be treated with calcium-based phosphorus binders throughout the pregnancy but this is not commonly needed due to increased removal following dialysis. There is limited data available regarding the use of other types of phosphorus binders.

Vitamin D deficiency should be addressed. Calcitriol has been used in pregnancy but it remains category C. Additional calcium supplementation of 1.5-2 g daily is recommended to meet fetal needs. The developing fetus requires approximately 30 grams of calcium for development. Although hypocalcemia is a concern, the patient should

also be monitored for hypercalcemia as this can cause restricted development of the fetal parathyroid gland.

Nutrition

The pregnant ESRD patient needs proper nutrition to support the development of the fetus and maintain weight gain. Most dietary restrictions are relaxed due to intensified dialysis. The patient must be encouraged to have nutritious and well-balanced meals, targeting adequate calorie and protein intake. Some removal of water-soluble vitamins with dialysis is anticipated, thus post-dialysis supplementation is recommended for all prenatal vitamins.

Ideally, the target of protein intake is 1.5-1.8 g/kg pre-pregnancy weight/day +20 g/day with calories increased to 25-35 kcal/kg/pregnant weight/day [2].

Hypertension

Hypertension (HTN) is one of the most commonly associated symptoms of a complicated pregnancy as well as ESRD. Hypertensive disorders are present in approximately 6-8% of pregnancies [1]. Differentials such as pre-eclampsia and HELLP syndrome are always high in these cases [28]. Medications should be reviewed if pregnancy is suspected. Many common medications used in the ESRD like ACE inhibitors (Angiotensin-Converting Enzyme Inhibitors) and ARBs (Angiotensin-Receptor Blockers) are teratogenic. Most antihypertensive do cross the placental barrier and cause adverse effects on the fetus. Antihypertensives found safe and effective for use during pregnancy include labetalol, methyldopa and nifedipine [29]. Care should be taken to control blood pressure yet prevent hypotension.

Blood Pressure (BP) control target ideally would be <140/80 mmHg. This target is meaningful as hypertension and hypotension put patient at increased risk. Significant elevation in BP put the mother at increased risk for stroke and abnormally low BP can impact the perfusion to the placenta, risking the developing fetus. HTN that remains uncontrolled does place the fetus at a decreased risk for survival. Antihypertensive treatment in pregnancy should be initiated if BP is consistently over 160/110. Women with a history of HTN prior to pregnancy may require a change in therapy due to potential medication adverse effects on the fetus as previously noted.

For patients with significantly elevated blood pressure, Complete Blood Count (CBC) should be monitored for hemolytic anemia, thrombocytopenia, and elevated liver enzymes.

Diabetes

Diabetic patients from a large cohort of ESRD patients, and have a challenging course with multifactorial complicating factors. Uremic milieu contributes to insulin resistance while endogenous insulin tends to stay in the system longer with renal failure [28]. Insulin is not removed on dialysis. These patients are at high risk for both hyperglycemia and hypoglycemia. Hyperglycemia is known to have an association with fetal compromise and birth defects, while hypoglycemia can compromise both maternal and fetal well-being. Good control of diabetes would contribute to better fetal outcomes such as preventing macrosomia, pregnancy loss/spontaneous abortion, preeclampsia, premature delivery, fetal demise, hypoglycemia and hyperbilirubinemia in the neonate and congenital deformations [1,30,31]. Initiation of insulin early on with adequate dosing is recommended. Best glycemic control is identified as glycated hemoglobin A1C (HbA1C) of 6-7% while preventing hypoglycemia in patients with Diabetes type 1, Diabetes type 2 or gestational diabetes [31,32]. This is a slightly

more stringent recommendation than for the general population due to the increased risk of the negative impact that high glucose levels have on the fetus. Target glucose levels are fasting <95 mg/dL and 1-hour postprandial <140 mg/dL or 2-hour postprandial <120 mg/dL. HbA1C though not very accurate in ESRD population, remains the preferred lab for long term glycemic control assessment. Close collaborative ties with endocrine specialists is highly recommended especially as some medications are unsafe to the fetus [25,33]. Insulin does not cross the placenta to a measurable extent and remains the gold standard in diabetes treatment during pregnancy. Metformin and glyburide do cross placenta but are considered acceptable and are used in pregnancy. They have equivalent effectiveness control of glucose levels as well as low risk to the mother and fetus [1]. All oral agents lack long-term safety data [31]. Metformin, though dialyzable with conventional dialysis, is not removed well with PD. Though this raises concern regarding metformin-induced lactic acidosis, data does not reflect that this concern is well-founded [34]. PD may provide some protection against this anticipated lactic acidosis [34,35]. Glyburide is unlikely to be dialyzable through PD, and not dialyzable on HD [36].

Immunosuppression in pregnancy and dialysis

Cyclosporine, tacrolimus, azathioprine, and prednisone are considered relatively safe during pregnancy but immunosuppressants do cross the placental barrier. There is not much data available regarding dialysis. Azathioprine is on the list of dialyzable drugs through conventional HD but not through PD, cyclosporine and prednisone are considered non-dialyzable through HD and PD. Tacrolimus is non-dialyzable on HD and unlikely to be on PD also [36]. Cyclosporine has been associated with prematurity and growth retardation, while tacrolimus has been associated with hyperkalemia and renal insufficiency in the fetus. Adrenal insufficiency and thymic hypoplasia have occasionally been described in the infants of transplant recipients but are unlikely if the dose of prednisone has been decreased to 15 mg [30].

Mycophenolate mofetil and sirolimus are contraindicated in pregnancy. Comanaging the patient with a high-risk obstetrician and transplant nephrologist is of paramount importance [30,37,38].

Obstetric care

These high-risk pregnancies include fetuses developing in mother with compromised health. Multispecialty care is essential. Diagnosing preeclampsia in anuric patients is challenging, as neither proteinuria nor impaired renal function can be used as a means of diagnosis. A placental ultrasound around 22 weeks with uterine and umbilical doppler to assess placental size and morphology and to quantify pulsatility indices can be used. Abnormal pulsatility indices combined with fetal growth restriction indicates a diagnosis of preeclampsia [27]. Though not widely available, antiangiogenic and angiogenic factor measurements, including soluble fms-like tyrosine kinase and placental growth factor may be used to aid in the diagnosis of preeclampsia. Use of magnesium for treatment will require caution due to possible toxic potential [39]. There are case reports addressing the use of apheresis to help remove this to aid the continuation of pregnancy [40].

Cervical cerclage may be required to treat early cervical incompetence and prevent preterm birth, reasons for which are unclear [14].

Planned delivery (preferred vaginal) around 37 weeks is the best-case scenario. Post-delivery monitoring of the neonate for at least 48 hours is usual care. Postpartum dialysis also has to be closely

monitored as the patient may now have a healing obstetric scar with high risk for bleeding.

Breast feeding

The benefit of breastfeeding supersedes any associated risk. Significantly higher levels of creatinine, urea and uric acid were found in pre-HD breast milk when compared to post-HD [39]. Sodium and chloride was significantly increased in post-HD samples. Phosphate was significantly lower in pre- and post-HD breast milk when compared to controls (low-risk mothers matched for postpartum age), whereas calcium showed no significant differences [39]. In terms of nutrient components, glucose levels were decreased, whereas protein, triglycerides, cholesterol and immunoglobulins were similar to control breast milk and were not affected by dialysis [39]. No significant differences were found in iron, potassium, and magnesium content [39]. Overall, there was a high similarity of HD patient breast milk to samples from low-risk control mothers [39]. Significant variations in the breast milk composition between pre- and post-HD samples suggests that breastfeeding after a dialysis session is preferable to breastfeeding prior to a dialysis session. The authors of the referenced work suggest discarding milk pumped immediately prior to dialysis [39].

There is no available data on breastfeeding in PD. There is an assumption that similar changes can be expected, without major variations due to the continuous nature of dialysis. In this case, the timing of breastfeeding would not be relevant.

Lactation safe medications for hypertension and comorbid conditions will be needed which include methyldopa, labetalol, or nifedipine. Methyldopa, though the best recommended for this period, does have the potential of causing further depression in the mothers, who are already in a high-stress situation. Captopril, enalapril, and quinapril are the preferred ACE inhibitors to use in the post-partum period as they are not secreted in breast milk [4, 41]. Close assessment for hypotension in the neonate is needed if these medications are initiated. Aggressive ultrafiltration may reduce milk supply. Avoiding heparin containing the preservative benzyl alcohol is prudent as it is potentially toxic to at-risk infants [42].

Emotional support

It is evident that pregnant women with ESRD face multiple extremely unique challenges. Difficulty in conception and maintaining pregnancy, caring for an infant and managing chronic illness and dialysis schedule require significant coping skills and support. There are multiple providers involved and ideally, the patient would be under the combined care of obstetrics and nephrologists. The newborn may also require medical care or prolonged hospital admission. This situation would likely be overwhelming for any new mother. Postpartum depression should be expected and treated early. Supportive care and counseling should be offered. There is a need for early discussions regarding childcare, education regarding post-pregnancy needs, and addressing practical advice for anticipated needs. Data is lacking in this area. Emotional support must be included in the care families facing these circumstances.

Future Research

Further research on the topic of pregnancy in ESRD and dialysis is needed [43]. A survey of American nephrologists revealed approximately 30% of respondents were not comfortable in the care of these patients, slightly more than 30% of respondents did report confidence in caring for this population and approximately 45% reported taking care of pregnant women receiving dialysis within

Table 3: Three pronged approach to pregnancy on dialysis.

Educate	Treat	Support
<p>Pre-plan and educate all potential ESRD patients desiring pregnancy regarding complexities, expectations and outcomes. Assess all women <50 or not menopausal, regarding desire for pregnancy and use of contraception.</p> <p>Consider conversations regarding adoption and surrogacy.</p>	<p>Intensify dialysis targeting about 36-40 hours per week. For PD, consider combined modality if clearance is borderline.</p> <p>Medication reconciliation: Increase supportive medications like ESA, iron, calcium. Expect decrease in phosphorus. Discontinue medications like ACE/ARB. Consider having a pharmacist review medications for potential risks to fetus.</p>	<p>Establish 7 specialist multidisciplinary care team early.</p> <p>A. Nephrologist B. Advanced Practice Registered Nurse (APRN)/ dedicated nursing staff who knows the patient well. C. Dietician D. Social Worker E. Mental health provider F. High risk obstetrician G. Neonatologist</p> <p>Anticipate postpartum complications.</p>

the last 5 years [3]. Most renal societies are encouraging dedicated research in this area. Topics include improving biomarkers of pregnancy-associated complications such as pre-eclampsia, early management techniques including apheresis, optimization of dialysis and early transplantation are all areas that necessitate further research. Data is lacking in the societal supports available for this population and exploration of alternative methods of family planning. Methods such as surrogacy and adoption should be added to this discussion. Most research has been focused on attempting to sustain a high-risk pregnancy known for adverse outcomes. Optimal quality of life should provide the patient with options. This review validates that pregnancy in ESRD and dialysis has made many advances over the past decades but there continues to be a substantial risk to the mother and fetus (Table 3).

Hence, dialysis in pregnancy is a complex healthcare issue that needs a multidisciplinary approach and clear understanding of the patient, their medical condition, and associated risks.

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