Renal disorders in pregnancy

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Abstract: Renal disorders in pregnancy are common. In high income countries, approximately 3% of pregnant women have chronic kidney disease (CKD) and often it is recognized for the first time during pregnancy. Approximately one fifth pregnant women developing preeclampsia before 30 weeks' gestation have previously undiagnosed CKD, especially those with severe proteinuria. Defining and staging CKD in pregnancy is challenging: from one hand physiological hyperfiltration might significantly alter CKD staging. On the other hand, the application of equations for estimating glomerular filtration rate (GFR) is strongly discouraged during pregnancy. By analyzing data from the literature, it is reasonable to assume that serum creatinine and albuminuria should be considered the most appropriate tests both for diagnosing and monitoring pregnant women with CKD. Creatinine clearance is cumbersome and the collection of the 24-h urine sample is often inaccurate, while proteinuria is affected by several analytical pitfalls. Serum creatinine should be measured by traceable methods in order to make comparable results between different laboratories. Albuminuria can be screened by dipstick methods; however, any positive result must be confirmed by a quantitative measurement either on a 24-h urine sample or on a first morning urine sample, reporting results as albuminuria-to-creatininuria ratio. Nephelometric methods for albuminuria enable an accurate measurement even in a range of 5–15 mg/L. Any negative dipstick result must be carefully evaluated on the basis of history and clinical signs, tacking into account possible false negative results due to the presence of a protein mixture constituted either by a very low concentration of albumin or by globular proteins only. Cystatin C should be used in the first trimester to predict the risk of preeclampsia and that of gestational diabetes mellitus. Finally, pregnant women with proteinuria must be periodically checked for urinary tract infection (UTI) by urine cultures.

Keywords: Pregnancy; chronic kidney disease (CKD); creatinine; creatinine clearance; proteinuria; albuminuria; cystatin C

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Introduction

Pregnancy is a special temporary life phase characterized by a myriad of physiological alterations, primarily involving vascular and hemodynamic changes. By 6 weeks of gestation, systemic vascular resistance decreases and arterial compliance increases, prior to the establishment of the uteroplacental circulation (1). By the second trimester, mean arterial blood pressure falls by an average of 10 mmHg below non-pregnant levels with mean values of 105/60 mmHg; concomitantly, sympathetic activity increases, mirrored in a 15% to 20% increase in heart rate (2). In the early first trimester, the association between decreased afterload with increased heart rate leads to a large increase in cardiac output, which peaks at 50% above pre-pregnancy levels by the middle of the third trimester (3). Clearly, these modifications predominantly involve kidney structure and functions, yielding relevant biochemical perturbations (4). The latter are associated with the endocrine re-modulation triggered by the egg fertilization and continuing over gestation until childbirth. Thus, it is not surprising the key role of laboratory medicine in managing pregnancy by biochemical and molecular diagnostic tests. Physiological uncomplicated pregnancy induces reversible anatomical and functional renal alterations. On the other hand, the kidney is specifically exposed to complications correlated with gestation, including: hypertension; preeclampsia; urinary tract infections; acute kidney injury (AKI); asymptomatic hematuria and proteinuria; drug-induced renal fetal toxicity; placenta accreta; and, less frequently, obstructive uropathy (5-13). In addition, pregnancy could exacerbate pre-existing specific kidney diseases, including chronic kidney disease (CKD), end stage kidney disease (ESKD), diabetic nephropathy, renal transplantation, lupus nephritis, antiphospholipid antibodies syndrome, focal segmental glomerulosclerosis, minimal change disease, membranous nephropathy, IgA nephropathy, atypical hemolytic-uremic syndrome (aHUS), and sclerodermia (14,15). In this review, we illustrate the clinical laboratory approach for assessing and monitoring renal metabolic physiology and kidney diseases during pregnancy.

Anatomical adaptations of the kidney in pregnant women

During pregnancy, the kidney increases by 1 to 1.5 cm in length and by up 30% in volume and decreases in size over a period of 6 months postpartum (3). Moreover, pregnancy induces physiologic dilation of the urinary collecting system that in turn generates hydronephrosis in up to 80% of women. Hydronephrosis is detectable in 43% to 100% pregnant women and is correlated with gestational age: the peak is reached at 28 weeks, with a 63% overall incidence (16). A right-sided preponderance of hydronephrosis could be observed in up to 86% of pregnant women. Since the dilated collecting system can hold 200 to 300 mL of urine, urinary stasis takes place, leading to a 40% increased risk for pyelonephritis with asymptomatic bacteriuria (17). These changes are likely due to mechanical compression of the ureters between the gravid uterus and the linea terminalis. Changes in hormonal levels, namely estrogen and progesterone, and the abundance in prostaglandins synthesis may also contribute to affect ureteral structure and peristalsis. However, no significant correlation has been ever demonstrated between progesterone or estrogen levels and severity of calyceal dilatation (18).

Glomerular filtration rate (GFR) in physiological, uncomplicated pregnancy

GFR defines the flow of plasma from the glomerulus into Bowman's space over a given period of time. Specifically, GFR enables to detect and monitor the capacity and the efficiency of the glomerulus in producing an ultrafiltrate from plasma (19). GFR is considered the best overall index of kidney function for two main reasons: firstly, most other kidney functions decline as GFR decreases; in addition, GFR decline is almost always associated with renal tissue injury and with alterations of microvascular bed (20). Clearance is the virtual plasma volume from which a solute is removed per unit time, expressed in milliliter (mL) per minute. Basically, glomerular filtration is a passive process depending on the balance between hydrostatic and osmotic forces; thus, intra-glomerular hydrostatic pressure strongly influences plasma filtration. In the mid seventies, an early study revealed the mechanistic basis of glomerular hemodynamics (21). On one hand, a close relationship was demonstrated between arterial blood pressure with the rate of plasma filtrated through Bowman's membrane. On the other hand, blood flow was found dependent upon the rate of pressure decrease along the length of the vessel. An additional significant factor involved in the modulation of the flow rate is the resistance offered by the vessel wall. Later, further studies elucidated the interplay between factors affecting microvascular dynamics (22,23). In 1951, an early study reported that both glomerular filtration rate (GFR), estimated by inulin clearance, and renal plasma flow (RPF), estimated by the paraamino hippurate (PAH) clearance, increase during pregnancy (24). Further studies confirmed this finding, demonstrating that the increase in RPF exceeded that of GFR in the early stages of pregnancy (60–80% and 40–60%, respectively) until RPF falls very quickly in the third trimester (25,26). Consequently, the decrease in filtration fraction (FF) is recognizable until the third trimester, before starting to increase. Usually, the increase in GFR reaches the peak during mid gestation (27) and thus this distinctive phenomenon of hemodynamic adaptation has been termed as midterm renal hyperfiltration (MRH). A GFR value >120 mL/min

Table 1 Hemodynamics indexes during normal, uncomplicated pregnancy

	Blood pressure[a]		GFR[b]	RPF[b]	FF[b]
	Systolic	Diastolic			
First Trimester (1–12 weeks)	111.5	65.2	+37%	+41.2%	−1.89%
Second Trimester (13–25 weeks)	110.0	64.0	+38.4%	+29.4%	+10.7%
Third Trimester (26–36 weeks)	115.0	69.0	+39.5%	+10.4%	+29.3%

GFR, glomerular filtration rate; RPF, renal plasma flow; FF, filtration fraction. aBlood pressure expressed as mmHg; data from 7,504 nulliparous and multiparous women with normal pregnancy (29); bmean values expressed as % variation above (+) or below (–) non-gravid levels.

per 1.73 m^2 is widely accepted as a criterion for normal MRH (28). The renin-aldosterone-angiotensin system and the relaxin pathway are strongly involved as potential inducers of MRH (29). During pregnancy, the progressive increase of GFR suggests a progressive utilization of the renal functional reserve, induced by gestation; however, only women with an intact renal functional reserve can increase their GFR during pregnancy (30). Recent studies found adverse pregnancy outcomes when MRH is either <120 mL/min per 1.73 m^2 or >150 mL/min per 1.73 m^2; these studies showed a positive correlation between GFR <120 mL/min per 1.73 m^2 and fetal growth, even in women without preeclampsia (31,32). The increase in blood pressure during late pregnancy, counterbalanced by the absence of a parallel increase of cardiac output, induces a progressive vascular resistance. Constriction of the efferent arteriole as part of this process may be the main source of the observed decrease in RPF associated with the decrease in GFR during late pregnancy (33). Two equally rigorous studies found that the decrease in FF, due to the greater increase in RPF compared with that of GFR, is limited within the first 12 weeks of gestation; afterward, FF progressively increases over the second and the third trimesters, reaching the peak at term (34,35). In conclusion, during pregnancy the rising GFR is closely related with: (I) the increase of the effective renal plasma flow; (II) the increase in transcapillary pressure gradients; (III) the increases in the ultrafiltration coefficient (36). *Table 1* summarizes data from the literature on systolic and diastolic blood pressure (37) during pregnancy and the corresponding increases and decreases of GFR, RPF, and FF.

Serum creatinine and creatinine clearance during pregnancy: advantages and pitfalls

In 1955, Homer Smith firstly postulated that a substance must fulfill several requirements in order to be accepted as valid for the measurement of GFR (38); unfortunately, this ideal biomarker does not exist. Despite considerable efforts over the last 50 years in searching endogenous and exogenous biomarkers for GFR, even in pregnant women (39), serum creatinine remains the most widely used biomarker for assessing kidney function worldwide (40). Perhaps, the most important limitation of serum creatinine consists of its non-linear relationship with GFR. During uncomplicated pregnancy, serum creatinine falls to 0.4–0.6 mg/dL (35–55 µmol/L) (41); this change reflects not only the pregnancy-induced increase in GFR, but also hemodilution deriving from approximately 30–50% plasma volume expansion, necessary for the greater circulatory needs of the maternal organs (42,43). Several studies attempted to establish age-specific serum creatinine changes reflecting the increase in glomerular hyperfiltration with advancing gestational age; regrettably, serum creatinine cut-off values and reference ranges vary between studies (44-47). For example, these studies reported different upper limits: 1.00 mg/dL (89 µmol/L) (45), 0.81 mg/dL (72 µmol/L) (46), and 0.90 mg/dL (80 µmol/L) (47). One of the most cited studies from the literature, including only 29 healthy pregnant women with an uncomplicated pregnancy, reported an upper limit of 1.07 mg/dL (95 µmol/L) (48). A number of analytical and clinical variables influence the high heterogeneity of these results, such as the choice of creatinine assay method (colorimetric Jaffe, enzymatic, dry-chemistry), the publication of results obtained by untraceable methods, the type of sample (plasma, serum, whole blood), the posture of pregnant women and its effects on renal plasma flow and GFR (49,50). In addition, a systematic analysis from the literature reveals that many authors omit to detail both the analytical method and how creatinine reference intervals have been derived, including whether or not they were specific to a female population. Discrepancies are exacerbated by the publication of serum creatinine reference ranges and cut-off levels based on personal experiences rather than experimental studies using standardized, traceable methods and large cohorts of pregnant women. Accordingly, serum creatinine reference

Table 2 Synthesis of results obtained by the systematic review on serum creatinine in pregnancy (56)

Serum creatinine in pregnancy	First Trimester	Second Trimester	Third Trimester
Mean values expressed as % of non-pregnant mean values	84%	77%	80%
97.5th centile (upper limit of the 95% reference range) expressed as % of non-pregnant 97.5th centiles	85%	80%	86%
Mean values based on female reference ranges (non-pregnant women)*	0.63 mg/dL (56 µmol/L)	0.59 mg/dL (52 µmol/L)	0.61 mg/dL (54 µmol/L)
Values outside the upper limit of normal for pregnancy expressed as mg/dL (mmol/L)	0.86 mg/dL (76 µmol/L)	0.81 mg/dL (72 µmol/L)	0.87 mg/dL (77 µmol/L)

*Female serum creatinine reference ranges published by Mazzacchi *et al.* (57).

ranges have been fixed 0.40–0.80 mg/dL (35–71 µmol/L) (51) and an undefined "mean value of serum creatinine during pregnancy" was established to be 0.60 mg/dL (53 µmol/L) (52). A serum creatinine value >1.0 mg/dL (>88 µmol/L), that is within reference ranges in healthy adults, was suggested as significant for unveiling renal impairment in the pregnant population (53); later, it was recommended that the suspicion of an early kidney injury during pregnancy should arise when serum creatinine exceeds the cut-off level of 0.85 mg/dL (75 µmol/L) (54). A recent meta-analysis compared serum creatinine and creatinine clearance reference ranges in non-pregnant women with those in healthy pregnant women over gestation (55). The meta-analysis included 29 published studies (globally: 376 non-pregnant and 1,037 healthy pregnant women). At <14 weeks' gestation, the mean relative difference in serum creatinine between pregnancy and reference values in non-pregnant women was −16.5%; at 15–21 weeks −23.2%, reaching a plateau at 22–28 weeks (−22.6%). At 29–35 weeks, the difference dropped to −15.5% and then showed a negligible increase until the end of pregnancy, with a mean difference of −17.7% (55). Another systematic review on serum creatinine in healthy, uncomplicated pregnancy compared results obtained in pregnant cohorts with either creatinine levels derived from a matched nonpregnant cohort or a local laboratory reference range (56). Forty-nine eligible studies were included in this analysis and data were divided by trimester of pregnancy: <13, 13–26, and >26 weeks, corresponding to 22 studies with 1,699 creatinine measurements, 28 studies with 2982 creatinine measurements, and 40 studies with 3978 creatinine measurements, respectively. Most relevant results have been summarized in *Table 2*. Based on serum creatinine reference ranges in females (0.51–1.02 mg/dL corresponding to 45–90 µmol/L), previously published in the literature (57), authors concluded that during pregnancy a serum creatinine level greater than 0.87 mg/dL (77 µmol/L) should be considered outside the normal range for pregnancy and should raise suspicion of either undiagnosed CKD before conception or early development of acute kidney injury (AKI). This cut-off is almost identical to that recommended three years earlier by Lightstone *et al.* (54). In a study on 243,534 Canadian pregnant women aged 16–50 years, serum creatinine was measured before, during, and after pregnancy (58). Prior to pregnancy, the mean serum creatinine concentration was 1.41 mg/dL, quickly dropping by four weeks into the pregnancy; between 16 and 32 weeks, the mean value was 1.11 mg/dL, then slowly rose to a maximum of 1.51 mg/dL a few weeks after delivery. Finally, by 18 weeks after delivery, a gradual return to mean concentrations prior to the pregnancy was observed. In *Table 3*, we have reported serum creatinine centiles found in that study. Regrettably, the study has several limitations, including the lack of any information on the analytical method used by authors as well as on whether or not the method was changed or modified during the study (April 2006 – March 2015). The clinical reliability of twenty-four hours (24-h) creatinine clearance, a historical, traditional laboratory test (59), is strongly debated in the literature. On one hand, many researchers consider creatinine clearance as a standard method for documenting glomerular function in clinical practice, even during pregnancy (60). On the other hand, several authors report that this functional test does not meet criteria for accuracy due to large systematic bias and imprecision (61). Creatinine clearance is convenient and widely used worldwide at least for four major advantages: in normal pregnancy, muscle mass is stable and does not affect urinary creatinine excretion (62); creatinine metabolism and elimination are significantly altered only by kidney impairment or systemic disorders such as cancer; the

Table 3 Serum creatinine percentiles pre-pregnancy (42,399 measurements), during pregnancy (244,866 measurements) and post-pregnancy (74,680 measurements), according to Mazzacchi *et al*. (57)

Timing (weeks)	50th centile, mg/dL [μmol/L]	75th centile, mg/dL [μmol/L]	95th centile, mg/dL [μmol/L]
Baseline pre-pregnancy	0.67 [59]	0.75 [66]	0.87 [77]
4th week	0.66 [58]	0.72 [64]	0.85 [75]
8th week	0.56 [50]	0.63 [56]	0.73 [65]
12th week	0.53 [47]	0.59 [52]	0.69 [61]
16th week	0.51 [45]	0.56 [50]	0.67 [59]
20th week	0.51 [45]	0.56 [50]	0.67 [59]
24th week	0.51 [45]	0.55 [49]	0.67 [59]
28th week	0.50 [44]	0.56 [50]	0.67 [59]
32nd week	0.51 [45]	0.56 [50]	0.68 [60]
36th week	0.54 [48]	0.61 [54]	0.74 [66]
40th week	0.60 [53]	0.69 [61]	0.86 [76]
2nd week postpartum	0.69 [61]	0.79 [70]	0.94 [83]
4th week postpartum	0.71 [63]	0.79 [70]	0.94 [83]
8th week postpartum	0.70 [62]	0.78 [69]	0.93 [82]

contribution of fetal creatinine is negligible (63); potentially interfering drugs on creatinine tubular excretion (e.g., cimetidine, trimethoprim-sulfamethoxazole) are not commonly used during pregnancy. The most important limitation of creatinine clearance depends upon critical issues affecting three elements: timed urine sample collection, biological variables, and standardization of analytical methods. Generally, timed (24-h) urine collection is often inaccurate, especially in the outpatient setting (64). Patients fail to follow standardized procedures for the collection, storage, and transport of urine samples (65). A widespread error is negligence either to collect the entire urine volume over 24-h or to collect the excess of sample. If the 24-h urine sample has not been completely and properly collected, creatinine clearance could be falsely decreased. Loss of specimens from poorly sealed containers, as well as the lack of time- and temperature-controlled transport may also give rise to incorrect results. Accurate timed urine collection is particularly crucial in pregnant women because of urine retention due to physiological hydronephrosis; indeed, significant amounts of urine may remain in the dilated collecting system. To reduce this error, pregnant women should be well hydrated and should rest on their left side for one hour before starting and completing the 24-h urine collection (50). Biological variables, such as diet, muscle mass, physical exercise and creatinine tubular secretion can significantly increase the creatinine clearance inaccuracy; in particular, tubular secretion of creatinine is the most important factor inducing an overestimation of GFR by approximately 10% to 20%. Furthermore, a growing kidney functional impairment over time induces a progressive increase in creatinine tubular secretion, masking a true drop-in GFR. In the past, GFR overestimation due to creatinine tubular secretion was roughly compensated with serum creatinine overestimation detectable by colorimetric Jaffe assays. With the implementation of traceable methods for serum creatinine, this unconventional 'compensation' is now reduced and overestimation of GFR by creatinine clearance will be no longer mitigated. Finally, despite serum creatinine assay has been standardized and most of the in-vitro-diagnostic (IVD) companies have introduced isotope dilution-mass spectrometry (ID-MS) traceable standard calibrators in their commercial kits (66,67), interferences in both Jaffe and enzymatic methods continue to affect results (68). In addition, urinary creatinine assay is not yet traceable and is influenced by several urinary interfering substances (e.g., drugs and food metabolites); as a result, test accuracy and reproducibility are currently unsatisfactory, with further negative consequence on the reliability of creatinine clearance values

Table 4 Summary of data reported either by single studies (★) or meta-analysis and reviews (^) on 24-h clearance creatinine changes during normal, uncomplicated pregnancy

Year	Sample size (n)	Creatinine clearance (mL/min)			Ref.
		First Trimester	Second Trimester	Third Trimester	
1958	13	Unavailable	168 (117–203)[a]	152 (109–206)[a]	(34)★
1980	10	Unavailable	144±9.8[b]	Unavailable	(70)★
1981	9	118±17[c]	Unavailable	Unavailable	(71)★
1988	11, 8, 10	115 (77–153)[a]	135 (107–148)[a]	143 (106–195)[a]	(30)★
1990	11, 17, 27	125±10[c]	122±10[c]	118±10[c]	(44)★
2005	68, 64	Unavailable	145 (92–220)[a]	141 (84–207)[a]	(72)★
2008	Not rep.	151±11[c]	154±15[c]	129±10[c]	(73)★
2009	12	Unavailable	129±1 [b]	100±7[b]	(74)★
2009	Not rep.	69–140[d]	55–136[d]	50–166[d]	(75)^

Data from Ref. 44 reflect the average of 2-h creatinine clearance in the morning and 2-h creatinine clearance in the afternoon. Not rep., not reported [a]Median and (interquartile range); [b]Mean ± SEM (standard error of the mean); [c]Mean ± SD (standard deviation); [d]Reference ranges.

(69). Therefore, it is not surprising that results reported by studies from the literature on creatinine clearance during normal, uncomplicated pregnancy significantly differ each other. Early, pioneering studies on creatinine clearance in pregnant women were often weak because either incomplete (24-h creatinine clearance was investigated during one or two trimesters only) or enrolling a very small number of healthy pregnant women. In 1958, Sims and Krantz compared several indexes of renal clearance during pregnancy, including creatinine clearance (34). They enrolled 12 healthy pregnant women, performing serial measurements in each trimester. One woman was enrolled also in her second pregnancy. However, only four results were available in the first trimester, 16 in the second and 31 in the third. Later, a study on eight healthy pregnant women reported a creatinine clearance mean value of 120 mL/min and 137 mL/min at the fourth and at the twelfth week of gestation, respectively (27). Sometimes data from the literature may be confounding: in a paper published in 1990, 2-h creatinine clearance was determined during normal, uncomplicated pregnancy by collecting a first 2-h urine sample in the morning, a second 2-h sample in the afternoon and ultimately by computing the average creatinine clearance (44). *Table 4*, summarizes results obtained in several published studies on creatinine clearance during pregnancy; it is clearly evident the large heterogeneity among studies (30,47,70-74); in such cases, we extrapolated creatinine clearance values from raw data or from a graphical representation of the results. In a recent meta-analysis, aggregate data were reported every four weeks over pregnancy, and a corresponding plot with a curve fit weighted by inverse variance clearly demonstrated heterogeneity between studies (55). By extrapolating results from the plot representing aggregate data on creatinine clearance during pregnancy, the median and 5th – 95th centiles were 124 mL/min (106–142 mL/min), 132 mL/min (112–151 mL/min) and 90 mL/min (101–115 mL/min) at the 4th, 18th, and 36th week of gestation, respectively. Authors concluded that aggregate data used to create the creatinine clearance curve was unfit to serve as a reference curve. In addition, they observed a significant difference between GFR measured by inulin clearance and creatinine clearance ($P<0.001$); this finding is irreconcilable with previous conclusions stating that in healthy pregnant women, 24-h creatinine clearance closely approximates inulin clearance (42). Actually, creatinine clearance overestimates 10–15% GFR when compared with inulin clearance, and this bias is more pronounced at lower levels of GFR (75,76); however, this discrepancy derives only in part from creatinine tubular secretion (increased in kidney failure), being due, to some extent, to a statistical phenomenon known as regression to the mean (77). Despite these problems, creatinine clearance still remains a useful estimation of glomerular filtration in clinical practice.

Biomarkers-based equations for estimating GFR during pregnancy

Since the myriad of problems affecting serum creatinine and creatinine clearance, from long-time nephrologists have developed many equations based on serum biomarkers, in conjunction with several variables (e.g., age, gender, race) and anthropometric measures, such as body length, weight, and so on. Historically, serum creatinine has been included in these equations, and in particular, the so-called Schwartz's formula was widely used very early in clinical practice by pediatricians for assessing renal function in childhood (78). Over the last ten years, George Schwartz revised and implemented his original equation, also including serum cystatin C (79). The latter and other emerging biomarkers have been used either in new equations for adults and children or in equations previously developed with serum creatinine (80-82). Except for the Cockcroft-Gault formula, created for estimating creatinine clearance (mL/min) but not GFR (83), equations provide a value of glomerular filtration, expressed as mL/min/1.73 m^2 body surface area, called 'estimated GFR' (eGFR). The aim is to minimize the impact of variables affecting extra-renal factors of variability in serum creatinine concentration, miming a steady-state condition (84). The analysis of equations for estimating GFR lies beyond the scope of this paper and has been addressed by a recent comprehensive review (85); what really matters is that no equation for eGFR is suitable in pregnancy and thus, equations should not be used during pregnancy. Many studies investigated the correlation between eGFR, computed by various equations, and GFR measured by inulin clearance or other 'gold standard methods' (plasma clearance of ^{125}I-Iothalamate or non-radioactive Iothalamate, Iohexol, ^{51}Cr-EDTA, ^{99m}Tc-DPTA) during normal, uncomplicated pregnancy as well as in hypertensive or pre-eclamptic pregnant women (74,75,86-92). Most studies found that equations are less accurate than serum creatinine and 24-h creatinine clearance for estimating GFR during pregnancy. They found a significant bias (roughly 10–40%) between eGFR obtained by equations (Cockcroft-Gault, MDRD, CKD-EPI) and 24-h creatinine clearance or GFR measured by inulin clearance. Clearly, a number of variables associated with pregnancy, such as a non-steady-state condition, a "dynamic" and peculiar body surface area, and hyperfiltration strongly affect results obtained by equations. As a result, current consensus statements and official documents clearly discourage the use of equations during pregnancy, recommending serum creatinine and 24-h creatinine clearance (93,94). Taking into account limitations previously described for serum creatinine and creatinine clearance, recommendations may be interpreted as the lack of an 'ideal' biomarker of GFR for pregnant women.

The role of serum cystatin C in pregnant women with CKD

The notion that changes in serum level of certain low-molecular mass proteins depend on changes in GFR was developed more than 40 years ago, when β_2-microglobulin and α_1-microglobulin (protein HC) were found to be freely filtered by the glomerulus and then almost completely reabsorbed (>99%) by proximal tubular cells (95,96). Later, their diagnostic value in clinical nephrology was definitively established, especially for the introduction of reliable immunoassays for their measurement (97). Among these small proteins, cystatin C received major consideration as a candidate biomarker of kidney function. Cystatin C was firstly discovered both in human cerebrospinal fluid and in human urine (98,99), and the complete amino acid sequence was finally determined in 1981 by Anders Grubb and Helge Löfberg (100). Cystatin C is a cysteine proteases inhibitor encoded by the CST3 gene, a housekeeping gene located on chromosome 20p11.2; the mature, active form of this protein is a single non-glycosylated polypeptide chain containing 120 amino acid residues and produced at a constant rate (101). Since 1994, several immunonephelometric and immunoturbidimetric methods have been optimized on automated analytical platforms for measuring cystatin C in clinical practice (102,103); however, methods standardization was obtained only recently, with the development of an international standard calibrator and the re-formulation of reference intervals and quality specifications (104-106). Cystatin C is a reliable biomarker of kidney function: a great number of clinical studies in adults, children, and newborns have definitively confirmed that serum cystatin C is more sensitive than serum creatinine (107,108). Although cystatin C is not influenced by extrarenal factors affecting serum creatinine (tubular secretion, protein intake, muscular mass, physical exercise, malnutrition), other extra-renal variables could

Table 5 Serum cystatin C in normal uncomplicated pregnancy

Year	First Trimester		Second Trimester		Third Trimester		Ref.
	Sample size (n)	Serum cystatin C, mg/L	Sample size (n)	Serum cystatin C, mg/L	Sample size (n)	Serum cystatin C, mg/L	
2005	197	0.89±0.12[a]	197	0.65±0.14[a]	197	0.82±0.19[a]	(114)
2005	5	0.53*	68	0.61 (0.48–0.89)[b]	64	0.88 (0.46–1.35)[b]	(72)
2007	–	–	–	–	218	1.05±0.19[a]	(115)
2008	–	–	–	–	100	1.21 (1.02–1.37)[c]	(116)
2011	38	0.69±0.16[a]	32	0.78±0.26[a]	39	1.21±0.30[a]	(117)
2012	–	–	12	0.80±0.03[a]	12	1.13±0.06[a]	(122)
2016	48	0.58±0.08[a]	–	–	–	–	(118)
2017	124	0.48–0.80[d]	–	–	–	–	(119)
2017		0.70±0.14[a]		0.75±0.16[a]		1.19±0.23[a]	(120)
2019	–	–		0.41–0.94[d]		0.43–1.33[d]	(121)

[a]Mean ± SD (standard deviation); [b]Median and (2.5 – 97.5 centiles); [c]Median and (interquartile range); [d]Reference ranges. *mean value extrapolated from data reported by Akbari (72) in figure 1.

induce changes in cystatin C serum levels, such as age, race, sex, obesity, smoking, hyperthyroidism, cancer, therapeutic treatment with steroids, inflammation, diabetes (109-111). Cystatin C does not seem to cross the placental barrier; consequently, neonatal blood cystatin C reflects neonatal kidney function only (112). During normal, uncomplicated pregnancy, serum cystatin C levels are correlated with gestational age; at late stages of pregnancy and before delivery, cystatin C concentration is significantly higher than that in healthy non-pregnant women (113). Various studies attempted to establish cystatin C reference ranges during normal, uncomplicated pregnancy (72,114-121); they have been summarized in *Table 5*. Despite a visible heterogeneity among results, due to variables such as sample size, analytical protocols, source and type of cystatin C antibodies, inclusion/exclusion criteria, and differences in maternal age, lifestyle, and race, it is clear that cystatin C increases as gestational age advances during gestation. Notably, after cystatin C assay standardization, previous results should be evaluated with caution. An additional variable inducing differences in cystatin C serum levels during gestation is a twin pregnancy. Serum cystatin C was found higher in twin pregnancy compared with singleton pregnancy in the first trimester (0.84±0.10 mg/L, n=15 versus 0.66±0.008 mg/L, n=86), second trimester (0.86±0.15, n=19 versus 0.67±0.08, n=88), and third trimester (1.68±0.45 mg/L, n= 38 versus 1.16±0.26 mg/L, n=69). The magnitude of differences in cystatin C concentration between singleton and twin pregnancy does not match with corresponding differences in GFR, especially in the second and third trimester (123). Moreover, in the third trimester, cystatin C serum levels in twin pregnancy were found higher than those in preeclamptic women (123). Cystatin C can be used during the third trimester as a specific and sensitive biomarker for the detection of preeclampsia: a recent meta-analysis based on 27 studies found a mean difference of 0.40 mg/L (95% CI: 0.33–0.46 mg/L) between preeclamptic women and controls (124). The pooled sensitivity was 0.85 (95% CI: 0.79–0.89) and the pooled specificity was 0.84 (95% CI: 0.77–0.90). Cystatin C may be considered a candidate biomarker for the prediction of preterm delivery in severe preeclampsia. A preliminary study on 26 preeclamptic women suggested a cut-off level of 1.48 mg/L, obtained by using an automated immunoturbidimetric assay; this threshold discriminates risk of preterm delivery with a sensitivity of 0.80 and a specificity of 0.75 (125). Based on the notion that inflammation considerably contributes to preterm delivery, authors postulated that cystatin C might reveal unexplored inflammatory processes associated with preeclampsia. However, this hypothesis should be reconsidered after the evaluation of robust results obtained in larger cohorts of pregnant women with preeclampsia. In addition, the well-known high activity of cathepsin B in the third trimester of uncomplicated pregnancy is counterbalanced by a high level of cystatin C that exerts a fundamental, protective role as an inhibitor of proteolytic enzymes, promoting placental separation in the peripartum period (126). Thus, it is reasonable to assume that in the second part of the third trimester cystatin C serum level does not depend exclusively on kidney function. On the other hand, this claim may be, in part, supported by the absence of correlation between cystatin C and inulin clearance during the second and third trimester, previously observed in a small sample size of pregnant women (122). A further extra-renal factor modulating cystatin C serum levels is gestational diabetes mellitus (GDM). In a cohort of 111 Chinese pregnant women with GDM, observed between 24–28 weeks of gestation, median serum cystatin C concentration was 1.0 mg/L (interquartile range 0.8–1.8 mg/L), significantly higher than 0.7 mg/L (interquartile range 0.6–1.0 mg/L) found in 289 healthy pregnant women with normal glucose tolerance (127). A cut-off of 0.95 mg/L was associated with a sensitivity and specificity of 0.59 and 0.73, respectively. A cystatin C value >1.0 mg/L reflected a 5-fold increased risk of GDM in Chinese pregnant women after adjusting for body mass index (BMI), age, glycated hemoglobin (HbA_1c), and homeostasis model assessment of insulin resistance (HOMA-IR). This result confirms the relationship between cystatin C and insulin resistance. In conclusion, cystatin C may be used during pregnancy as a risk factor for predicting preeclampsia and GDM rather than a biomarker of GFR. Indeed, encouraging results suggest the clinical utilization of cystatin C, even in the first trimester for predicting gestational complications (128,129).

Proteinuria and albuminuria in pregnancy

As the nephrologist Arturo Borsatti used to say more than 30 years ago, proteinuria is always a critical condition both for physicians and patients (130). Proteinuria, that is the loss of proteins with the urine, is an unequivocal sign of kidney injury: it was defined as 'the clinical signature of podocyte injury', being mainly caused by defects in glomerular size-selectivity and charge-selectivity (131-133). However, proteinuria is associated with tubulointerstitial injuries due to various noxae such as acute tubular necrosis, nephritis, fever, nephrotoxic substances and drugs, cancer, and any other condition associated with hypoxia, ischemia, inflammation, and infection. Prolonged proteinuria induces severe parenchymal changes, including tubular epithelial cell apoptosis and the epithelial-to-mesenchymal transition (EMT). In definitive, proteinuria can take origin from an increasing glomerular filtration of circulating plasma proteins, almost completely retained within the blood circulatory system in physiologic conditions, or from impaired reabsorption of proteins by the proximal tubular cells. The two phenomena are related not only to each other; rather, they cohabit in the so-called glomerular proteinuria, marked by proteins in the urine with the size of albumin and larger. Proteinuria is a pathogenic factor in the progression of kidney dysfunction. In particular, proteinuria is strongly associated with the risk of CKD progression and is the most powerful predictor of ESKD risk over ten years (134). The clinical significance of proteinuria and albuminuria during gestation is crucial; they are potential risk factors for adverse maternal and neonatal outcome (135). For example, proteinuria is a hallmark of preeclampsia, even though proteinuria may be absent at the onset of the disease in up to 10% of pregnant women with preeclampsia and 20% with eclampsia (136). On the other hand, albuminuria reflects the severity and prognosis of gestational diabetes, being a marker of systemic endothelial cell dysfunction (137,138). In normal, uncomplicated pregnancy, a progressive increase in urinary excretion of total proteins is considered physiologic, especially after 20 weeks of gestation. Healthy pregnant women may double the reference range upper limit of healthy adults, and the increase is more pronounced in twin pregnancies (139). Hyperfiltration is the main factor associated with this physiologic increase. Tamm-Horsfall, a high molecular weight glycoprotein originating from the epithelial surfaces of the thick ascending limb of the loop of Henle and from the early distal convoluted tubule, is the most abundant urinary protein; in addition, small amounts of IgA, secreted by the renal tubule, albumin, and other plasma proteins may be recognizable. In healthy pregnant women, mean values of proteinuria and albuminuria correspond to 116.9 mg/24 h (upper 95% CI: 259.4 mg/24 h) and 11.8 mg/24 h (upper 95% CI: 28.7 mg/24 h), respectively (140). The American College of Obstetrics and Gynecology (ACOG) Hypertension in Pregnancy Task Force established that proteinuria in pregnancy corresponds to 'the new appearance of protein in the urine in amounts equal to or greater than 300 mg of protein in 24-hour collection, protein/creatinine (Cr) ratio equal to or greater than 0.3 mg/mg, or +2 or more on urine dipstick testing' (141). A tentative classification of proteinuria during pregnancy has identified four main classes: (I) isolated *de novo* proteinuria; (II) *de novo* proteinuria associated with preeclampsia; (III) proteinuria secondary to CKD; (IV) transient proteinuria due to urinary tract infection. Isolated proteinuria has been defined as the onset of new proteinuria (>300 mg/g Cr) without hypertension at any stage of gestation. It occurs in 13% of normotensive pregnancies and is associated with the development of hypertension; about 50% of pregnant women with isolated proteinuria develop preeclampsia, even in the absence of hypertension (142,143). It remains largely unclear what is the main factor inducing proteinuria in the absence of hypertension: findings on the relationship between high body mass index or low levels of circulating angiogenic factors (e.g., placental growth factor) and isolated proteinuria should be confirmed by further studies on larger cohorts of pregnant women (144). The appearance of proteinuria in the early stages of gestation (within 20 weeks) is mainly associated with preexisting diseases such as CKD, chronic hypertension, type 1 or 2 diabetes mellitus; in such a case, proteinuria has been called chronic proteinuria. If the onset of proteinuria occurs after 20 weeks of gestation, it is most likely that its origin may be gestational proteinuria or preeclampsia (143). Despite the clinical value of proteinuria, analytical methods for measuring urine total proteins are inaccurate and poorly reproducible. The most important limitation of methods for measuring urine total proteins is their inability to detect all types of proteinuria accurately. An emblematic example is the dipstick method, a very popular, inexpensive, semi-quantitative assay based on a colorimetric reaction (145). Dipstick recognizes exclusively the presence of albumin in the urine sample, leading to false-negative results when proteinuria consists of other types of proteins, such as transferrin, immunoglobulins, and low-molecular-mass proteins. In addition, very small amounts of albuminuria (approximately when <30 mg/L) cannot be accurately detected by dipstick methods. Since albuminuria represents a cardiovascular risk factor, even in the range of 5–30 mg/L, this limitation may be clinically relevant. On the other hand, dipstick enables the self-assessment of albuminuria, and this advantage is particularly useful in pregnant women at risk of hypertension or preeclampsia monitored on an outpatient basis. Any positive results obtained by the dipstick must be confirmed by a quantitative method either on a 24-h urine sample or on a spot urine sample in association with the determination of creatininuria. The former is considered the gold standard for the measurement of proteinuria and albuminuria; however, the 24-h urine collection is cumbersome and often inaccurate, leading to errors in results. Spot urine sample is simple to collect and evidence from the literature strongly suggests the collection of this type of sample during gestation (146-148). Results must be expressed as ratio proteinuria or albuminuria to creatininuria. Proteinuria can be quantitatively measured by chemical, turbidimetric, and dye-binding methods. Unfortunately, no reference measurement procedure has been established for urine total protein assay and available methods are affected by several drawbacks. For example, substances commonly present in the urine (inorganic ions, xenobiotics, drugs and their catabolites) can interfere in the chemical reaction. Moreover, the high heterogeneity of urine protein content corresponds to different dye-binding affinity; consequently, serial measurements may be imprecise, depending on differences in urine protein content over time. Ultimately, urine total protein assays are neither traceable nor standardized, leading to inaccurate and imprecise test results. Conversely, albuminuria can be measured by immunological methods optimized on automated analytical platforms. In particular, nephelometric immunoassays enable the accurate measurement of very small amounts of albuminuria (5–30 mg/L). In conclusion, quality specifications of albuminuria assays are significantly better than those of proteinuria and thus, albuminuria may be recommended as a test of choice for replacing proteinuria (149). In Chinese pregnant women, results within the range of 20–60 mg albumin/g creatinine accurately predict significant proteinuria and roughly correspond to more than 300 mg total protein/day by 24-h urine collection (150).

Chronic kidney disease (CKD) in pregnancy

The diagnosis and management of CKD in pregnant women is extremely challenging at least for 5 peculiar issues. Firstly, no early and specific clinical sign unveils the presence of kidney impairment; similarly, no biochemical test is available for an early and specific diagnosis of kidney disease. Second, kidney function during pregnancy cannot be assessed by equations developed for estimating GFR in adults and children. As already mentioned in this review, no equation has been definitively validated and the only reliable tests for evaluating glomerular filtration are serum creatinine and creatinine clearance (151). This limit hampers the application of the scheme for the evaluation of CKD staging based on the combination of eGFR and albuminuria values (152). Third, hyperfiltration during pregnancy might significantly alter CKD staging (153). Based on these limitations, defining and staging CKD in pregnancy is almost unachievable. Fourth, CKD in pregnancy is a severe risk factor for adverse maternal-fetal outcomes, including preeclampsia (PE), pregnancy-induced hypertension, anemia, and proteinuria as well as pre-term delivery, fetal growth restriction, low birth weight and the need of admission in neonatal intensive care unit (NICU) at birth (154). Women with advanced CKD are much less likely to have an uncomplicated pregnancy compared with women with normal kidney function. Ultimately, therapies commonly used in adults and teenagers with CKD are contraindicated in pregnancy, while no specific treatment for CKD in pregnancy exists (155). CKD in pregnancy might be assimilated to an idiomatic expression rather than a disease: actually, a wide range of pathological conditions could lead either to the development or to the worsening of the reduction in renal mass and the loss of renal reserve during pregnancy, such as: pre-existing CKD; primary glomerulonephritis (e.g., nephrotic syndrome, idiopathic membranous nephropathy, minimal change nephropathy, focal segmental glomerulosclerosis); diabetic nephropathy; IgA nephropathy; pyelonephritis; renal malformations; hypertension; systemic lupus erythematosus (SLE); autosomal dominant polycystic kidney disease (ADPKD). Nevertheless, the etiology of CKD in pregnancy has fewer effects on maternal-fetal outcomes than CKD stage, unless SLE nephritis, especially when associated with anti phospholipids antibodies (156). The only kidney disease associated with a high risk of extra-renal malformations is diabetic nephropathy (157). Very few robust data on the prevalence of CKD in pregnancy have been published; a consistent obstacle consists of the difficulty in the identification and definition of the early stage of CKD in pregnancy. Cumulative prevalence of CKD in pregnancy has been estimated at 3.3% in a Norvegian population, being 2.4%, 0.8%, and 0.1% in CKD stages 1, 2, and 3, respectively (158). CKD stages 3–5 have been estimated to affect one every 750 pregnant women (72). Approximately 20% of pregnant women developing pre-eclampsia before 30 weeks' gestation have previously undiagnosed CKD, especially those with severe proteinuria (72). All pregnant women with CKD should be monitored during gestation by a multidisciplinary team involving specialists in obstetrics, nephrology, urology, fetal medicine, and neonatology, being at risk for pregnancy-related adverse events. The frequency of follow-up must be adapted to the severity of the disease; for example, in CKD stages 3–5, follow-up should be intensified. Follow-up of pregnant women with CKD is basic for the early recognition and treatment of complications, including proteinuria, anemia, coagulation disorders, hypertension and systemic diseases. The onset of proteinuria during the third trimester can be due either to glomerular disease or to preeclampsia; thus it is mandatory a differential diagnosis, based on the evaluation of the balance between angiogenic-antiangiogenic patterns (soluble Fms-like tyrosine kinase, placental growth factor) as well as on impaired uteroplacental Doppler flows. Proteinuria should be carefully monitored in pregnant women with CKD, being more frequent in women already proteinuric at the start of gestation and increasing progressively in diabetic nephropathy. Kidney biopsy is not recommended in pregnancy, mainly for associated risks of severe bleeding complications (159). However, when kidney function declines progressively, especially during the first trimester, the pros and cons of renal biopsy versus empiric therapy should be carefully evaluated for each woman. On the other hand, in the third trimester, the medical team should evaluate the balance between the advantage of renal biopsy versus the risk of preterm delivery and adverse neonatal outcomes.

Conclusions

The role of laboratory medicine in managing maternal CKD during gestation is basic, especially at the early stage of the disease, when clinical signs and symptoms cannot be easily recognized. Optimal management of CKD during pregnancy depends on the choice of the right test performed in the right woman at the right time, interpreting results on the basis of specific analytical and clinical limitations. Serum creatinine and albuminuria should be considered the most appropriate tests both for diagnosing and monitoring pregnant women with CKD. Serum creatinine and albuminuria are more reliable than creatinine clearance and proteinuria, respectively. The former is cumbersome and the collection of the 24-h urine sample is often inaccurate; the latter is affected by several analytical pitfalls. Since the estimation of GFR by equations is not applicable during pregnancy, creatinine clearance may be of clinical value in certain conditions. However, to obtain a reliable creatinine clearance result, 24-h urine collection must be rigorous. Albuminuria can be screened by qualitative/semiquantitative dipstick methods; however, any positive result must be confirmed by a quantitative measurement either on a 24-h urine sample or on a first-morning urine sample by reporting results as albuminuria-to-creatininuria ratio. Any negative result obtained by dipstick must be carefully evaluated on the basis of history and clinical signs, tacking into account possible false-negative results due to the presence of a protein mixture without albumin or with a very low concentration of albumin. Cystatin C should be used in the first trimester to predict the risk of preeclampsia and that of gestational diabetes mellitus as well as the risk of complications in the third trimester. Finally, pregnant women with proteinuria must be checked for urinary tract infection (UTI) twice monthly, or weekly if necessary, by urine cultures (157). This recommendation is particularly fundamental in pregnant women with ADPKD, pyelonephritis, and renal malformation. The early recognition of UTI is crucial to avoiding the evolution of UTI in a chronic or recurrent infection that, in turn, induces a further increase in proteinuria as well as an increased risk of placental and fetal infections (160).

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Footnote

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