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Review Article

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A Review on Cystatin C and Fibroid

Obeagu Emmanuel Ifeanyi[1] and Obeagu Getrude Uzoma[2]

[1]Diagnostic Laboratory Unit, Department of University Health Services, Michael Okpara University of Agriculture, Umudike, Abia State, Nigeria.

[2]Department of Nursing Science, Ebonyi State University, Abakaliki, Nigeria.

*Corresponding author: *emmanuelobeagu@yahoo.com/obeagu.emmanuel@mouau.edu.ng*

Abstract

Cystatin C a protein encoded by the CST3 gene is mainly used as a biomarker of kidney function. Cystatin C levels have been reported to be altered in patients with cancer thyroid dysfunction and glucocorticoid therapy in some but not all situations. Cystatin C is an endogenous marker of renal function because of its stable production rate from all nucleated cells and its almost exclusive elimination from the circulation by glomerular filtration. Uterine fibroid (myoma or leiomyoma) are benign growths of smooth muscle and connective tissue anchored in the muscular wall of the uterus. Fibroids are the most common female pelvic tumor; their etiology is unknown. Biomarkers are sought to provide diagnostic as well as prognostic information. Ideally a good biomarker must be both reliable and reproducible. Cytatin C will be a strong biomarker in fibroid to check for changes to cancer and renal function in the patients.

Keywords: Cystatin C, Fibroid, Biomarkers, Pregnancy

Cystatin C

Cystatin C is a protein encoded by the CST3 gene is mainly used as a biomarker of kidney function. Cystatin C levels have been reported to be altered in patients with cancer (even subtle) thyroid dysfunction and glucocorticoid therapy in some but not all situations. Levels seem to be increased in systemic infection, which might or might not reflect actual renal dysfunction (Nnatuanya et al., 2017; Larson *et al*., 2004). The role of Cystatin C to monitor GFR during pregnancy remains controversial. Cystatin c is d in virtually all tissues and body fluids. It is a potent inhibitor of lysosomal proteinases (enzymes from a special subunit of the cell that break down proteins) and probably one of the most important extracellular inhibitors of cystein c proteases (it prevents the breakdown of proteins outside the cell by a specific type protein degrading enzymes) (Larson *et al*., 2004).

A substantial body of evidence has developed over the past several years which supports the use of Cystatin C as an alternative and more sensitive endogenous maker for the estimation of GFR than serum creatinine and serum creatinine based Glomerular filtration rate) GFR estimations

(Larson *et al.*, 2004). Cystatin C levels are less dependent on age, sex, race and muscle mass compared creatinine. Cystatin C measurements alone have not been shown to be superior formula-adjusted estimations of kidney function (Shlipak, 2007). As opposed to previous claims, cystatin C has been found to be influenced by body composition (Malcdonald *et al.*,2006; Shlipak *et* al., 2006). It has been suggested that cystatin C might predict the risk of developing chronic kidney disease, thereby signaling a of 'preclinical' kidney dysfunction (Hermida and Tutor, 2006).

Cystatin C as an endogenous marker of renal function

Cystatin C is an endogenous marker of renal function because of its stable production rate from all nucleated cells and its almost exclusive elimination from the circulation by glomerular filtration (Simonscn *et al.,* 1985 and Grubb, 2000). Its serum generally reflects the glomerular filtration rate more closely than creatinine (Grubb, 2000). A marker of kidney health is best measured by injecting compounds such as inulin, radioisotopes such as 51chromium-EDTA, 1251-iothalamate, 99mTc-DTPA or radiocontrast agents such as iohexol, but these techniques are complicated, costly, time-consuming and have potential side effects. Creatinine is the most widely used biomarker of kidney function. It is inaccurate at detecting mild renal impairment, and levels can vary with muscle mass but not with protein intake. Urea levels might change with protein intake. Cystatin C has a low molecular weight (approximately 13.3 kilodaltons), and it is removed from the bloodstream by glomerular filtration in the kidneys. If kidney function and glomerular filtration rate decline, the blood levels of cystatin C rise. Serum levels of cystatin C are a more precise test of kidney function (as - presented by the glomerular filtration rate, GFR) than serum creatinine level (King and Levey, 1993; Premaratne *et al.,* 2008).

Studies have also investigated cystatin C as a marker of kidney function in the adjustment of medication dosages (Larson *et* al., 2004). Cystatin C levels have been reported to be altered in patients with cancer, (even subtle) thyroid dysfunction and glucocorticoid therapy in some but not all situations (Larson *et al*.,2004) Levels seem to be increased in HIV infection, which might or might not reflect actual renal dysfunction. The role of cystatin C to monitor GFR during pregnancy remains controversial. Like creatinine, the elimination of cystatin C via routes other than the kidney increase with worsening GFR (Larson *et* a*l*., 2004).

Kidney dysfunction increases the risk of death and cardiovascular disease. Several studies have found that increased levels of cystatin C are associated with the risk of death, several types of cardiovascular disease (including myocardial infarction, stroke, heart failure, peripheral arterial disease and metabolic syndrome) and healthy aging. Some studies have found cystatin C to be better in this regard than serum creatinine or creatinine-based GFR equations. Because the association of Cystatin C with long term outcomes has appeared stronger than what could be expected for GFR, it has been hypothesized that cystatin C might also be linked to mortality in a way independent of kidney function. In keeping with its housekeeping gene properties, it has been suggested that cystatin C might be influenced by the basal metabolic rate.

Mutations in the cystatin 3 genes are responsible for the Icelandic type of hereditary cerebral amyloid angiopathy, a condition predisposing to intracerebral Hemorrhage, stroke and dementia. The condition is inherited in a dominant fashion. Since cystatin 3 also binds amyloid p and reduces its aggregation and deposition, it is a potential target in Alzheimer's disease. Although not all studies have confirmed this, the overall evidence is in favor of our role for CST3 as a susceptibility gene for Alzheimer's disease. Cystatin C levels have been reported to be higher in subjects with Alzheimer's disease. The role of cystatin C in multiple sclerosis and other demyelinating diseases (characterized by a loss of the myelin nerve sheath) remains controversial.

Cystatin C levels are decreased in atherosclerotic (so-called 'hardening' of the arteries) and aneurysmal (saccular bulging) lesions of the

aorta. Genetic and prognostic studies also suggest a role for cystatin C. Breakdown of parts of the vessel wall in these conditions is thought to result from an imbalance between proteinases (cysteine proteases and matrix metalloproteinases, increased) and their inhibitors (such as cystatin C, decreased). A few studies have looked at the role of cystatin *C* or the CST3 gene in age-related macular degeneration. Cystatin C has also been investigated as a prognostic marker in several forms of cancer.

Uterine fibroid

Uterine fibroid (myoma or leiomyoma) are benign growths of smooth muscle and connective tissue anchored in the muscular wall of the uterus (Wallach and Vlahos, 2004). Fibroids are the most common female pelvic tumor; their etiology is unknown. They develop from microscopic nests of uterine muscle cells and have been documented to be composed of numerous copies of the same or very few cells which is termed monoclonal expansion (Schwartz *et al.,* 2000). Uterine fibroids are benign smooth muscle tumors of the uterus. Most women have no symptoms while others may have painful or heavy periods. If they push on the bladder a frequent need to urinate may occur. Clinically they may initially be detected as small nodules identified only by imaging studies; they can potentially progress through a spectrum of growth from grape size to large masses that can be palpated through the abdominal wall. With that caveat, fibroids documented in treatment studies are often in the size range of 2 to 7.5 centimeters or the dimensions of a large marble to modestly smaller than a baseball (Wallach and Vlahos, 2004).

Architectural explanations, such as overall enlargement of the uterus by the size and number of fibroids, are often used to describe why fibroids cause common symptoms like heavy menstrual bleeding. Position and size with respect to other structures such as the bladder, bowel, vaginal vault, and nerve bundles in the pelvis are most often used to explain bulk symptoms (i.e., pressure, urinary frequency, constipation or pain with bowel movements, pressure or pain with intercourse, and more generalized pain symptoms). Nonetheless, many fibroids across a large range of sizes do not cause symptoms. The factors that determine which women develop symptoms are unknown.

Incidence is also poorly documented. However, cross-sectional studies, clinical databases, and case-control studies are investigating epidemiologic markers of risk of fibroids (Cramer *et al.,* 1995). Because fibroids arise after menarche and become largely quiescent after menopause, they clearly are subject to hormonal They are classified by their location relative to the layers of the uterus (as subserous, intramural, or submucous) and can be single or multiple. These kinds of lesions seem to arise from myometrial transformation as a result of specific physiological and pathological conditions. The majority of these monoclonal estrogen-dependent uterine neoformations afflict mostly women during reproductive age.

Location and classification

Growth and location are the main factors that determine if a fibroid leads to symptoms and problems (Wallach and Vlahos, 2004). A small lesion can be symptomatic if located within the uterine cavity while a large lesion on the outside of the uterus may go unnoticed. Different locations are classified as follows: Intramural fibroids are located within the wall of the uterus and are the most common type; unless large, they may be asymptomatic. Intramural fibroids begin as small nodules in the muscular wall of the uterus. With time, intramural fibroids may expand inwards, causing distortion and elongation of the uterine cavity. Subserosal fibroids are located underneath the mucosal (peritoneal) surface of the uterus and can become very large. They can also grow out in a papillary manner to become pedunculated fibroids. These pedunculated growths can actually detach from the uterus to become a parasitic leiomyoma.

Submucosal fibroids are located in the muscle beneath the endometrium of the uterus and distort the uterine cavity; even small lesions in this location may lead to bleeding and infertility. A pedunculated lesion within the cavity is termed an intracavitary fibroid and can be passed through the cervix.

Cervical fibroids are located in the wall of the cervix (neck of the uterus). Rarely, fibroids are found in the supporting structures (round ligament, broad ligament, or uterosacral ligament) of the uterus that also contain smooth muscle tissue. extrauterine fibroids of uterine origin: Metastatic fibroids of uterine origin located in other parts of the body, sometimes also called parasitic myomas have been historically extremely rare, but are now diagnosed with increasing frequency. They may be related or identical to metastasizing leiomyoma. They are in most cases still hormone dependent but may cause life-threatening complications when they appear in distant organs. Some sources suggest that a substantial share of the cases may be late complications of surgeries such as myomectomy or hysterectomy. Particularly laparoscopic myomectomy using a morcellator has been associated with a substantially increased risk of this complication (Nezhat and Kho, 2010). There are a number of rare conditions in which fibroids

metastasize. They still grow in a benign fashion, but can be dangerous depending on their location;
In leiomyoma with vascular invasion, an ordinary-appearing fibroid invades into a veessel but there is no risk of recurrence.
In intravenous leiomyomatosis, leiomyomata grow in veins with uterine fibroids as their source. Involvement of the heart can be fatal.
In benign metastasizing leiomyoma, leiomyomata grow in more distant sites such as the lungs and lymph nodes. The source is not entirely clear. Pulmonary involvement can be fatal.
In disseminated intraperitoneal leiomyomatosis, leiomyomata grow diffusely on the peritoneal and omental surfaces, with uterine fibroids as their source. This can simulate a malignant tumor but behaves benignly.

Signs and symptoms

Fibroids, particularly when small, may be entirely asymptomatic. Symptoms depend on the location and size of the fibroid. Important symptoms include abnormal uterine bleeding, heavy or painful periods, abdominal discomfort or bloating, painful defecation, back ache, urinary frequency or retention, and in some cases, infertility. There may also be pain during intercourse, depending on the location of the fibroid. During pregnancy, they may also be the cause of miscarriage, bleeding, premature labor, or interference with the position of the fetus (Wegienka *et al.*, 2003)

The proportion of women with fibroids who are symptomatic varies with the size and location of the fibroids with at least 60% of women suffering from one or more symptoms (Zimmermannn *et al.*, 2012; Kroon *et al.*, 2011). Fibroids may cause very mild symptoms, none at all or symptoms can be severe.

Pathogenesis

The exact cause of fibroids is not clearly understood, but the current working hypothesis is that genetic predispositions, prenatal hormone exposure and the effects of hormones, growth factors and xenoestrogens cause fibroid growth. Known risk factors are African descent, obesity, polycystic ovary syndrome, diabetes, hypertension, and never having given birth. Fibroid growth is strongly dependent on estrogen and progesterone. Although both estrogen and progesterone are usually regarded as growth-promoting they will also cause growth restriction in some circumstances. Paradoxically, fibroids rarely grow during pregnancy despite very high steroid hormone levels and pregnancy appears to exert a certain protective effect.

Fibroids are monoclonal tumors and approximately 40 to 50% show karyotypically detectable chromosomal abnormalities. When multiple fibroids are present they frequently have unrelated genetic defects. The exact cause of fibroids is not clearly understood, but the current working hypothesis is that genetic predispositions, prenatal hormone exposure and the effects of hormones, growth factors and xenoestrogens cause fibroid growth. Known risk factors are African descent, obesity, polycystic ovary syndrome, diabetes, hypertension, and never having liven birth.

It is believed that estrogen and progesterone have a mitogenic effect on leiomyoma cells and also act by influencing (directly and indirectly) a large

number of growth factors, cytokines and apoptotic factors as well as other hormones. Furthermore, the actions of estrogen and progesterone are modulated by the cross-talk between estrogen, progesterone and prolactin signaling which controls the expression of the respective nuclear receptors.

It is believed that estrogen promotes growth by up-regulating IGF-1, EGFR, TGF-betal, TGF-beta3 and PDGF, and promotes aberrant survival of leiomyoma cells by down-regulating p53, increasing expression of the anti-apoptotic factor PCP4 and antagonizing PPAR-gamma signalling. Progesterone is thought to promote the growth of leiomyoma through up-regulating EGF, TGF-beta 1 and TGF-beta3, and promotes survival through up-regulating Bcl-2 expression and down-regulating TNF-alpha.

Progesterone is believed to counteract growth by downregulating IGF-1. Expression of transforming growth interacting factor (TGIF) is increased in leiomyoma compared with myornelrium. TGIF is a potential represser of TGF-J3 pathways in myometrial cells. While fibroids are common, they are not a typical cause for infertility, accounting for about 3% of reasons why a woman may not be able to have a child. The majority of women with uterine fibroids will have normal pregnancy outcomes. In cases of intercurrent uterine fibroids in infertility, a fibroid is typically located in a submucosal position and it is thought that this location may interfere with the function of the lining and the ability of the embryo to implant. Also, larger fibroids may distort or block the fallopian tubes.

Risk Factors

The literature regarding predisposing risk factors for development of myomas should be interpreted with caution. Analysis is limited by the paucity of studies available, the study populations (mostly in Caucasian women), and the conflicting results, suggests other unexamined factors may be involved. The high background prevalence of fibroid, and possible detection bias as a consequence of increased medical surveillance of symptomatic women, may make interpretation of epidemiologic data difficult. The reliability of self-reported diagnoses may be questioned; the development of fibroid may have preceded the exposure to risk factors but may not have been recognized until after presentation to a healthcare provider. Prospective, longitudinal studies are underway to better characterize the factors that influence the development of uterine fibroid.

Age

Women are most likely to be diagnosed with fibroid during their forties; however, it is not clear whether this is because of increased formation or increased fibroid growth secondary to hormonal changes during this time (Marshall *et al,* 1998). Another factor that might distort the incidence may be the willingness of physicians to recommend, and for women to accept, hysterectomy only after they have completed the childbearing years (Endogenous hormonal factors. Early menarche (<10 years old) has been found to increase (relative risk [RR] 1.24) and late menarche (>16 years) to decrease (RR 0.68) the risk of uterine fibroid (Marshall *et al,* 1998). Fibroid are smaller and less numerous in hysterectomy specimens from postmenopausal women when endogenous estrogen levels are low; fibroid cell size is significantly smaller in postmenopausal women (Marshall *et al.1998).*

Family history

First degree relatives of women with fibroid have a 2.5 times increased risk of deveoping fibroids (Schwartz *et al.,* 2000; Vikhlyaeva *et* a*l*., 1995). Women Obesity findings have been reported in women with greater than 30% body fat. Obesity increases conversion of adrenal androgens to estrone decreases sex hormone-binding globulin. The result is an increase in biologically available estrogen, which may explain an increase in fibroid prevalence and/or growth.

Diet

Few studies have examined the association between diet and the presence or growth of fibroids. One study found that beef, other red meat, and ham increased incidence of fibroids, but green vegetables decreased it. These findings are difficult to interpret because the study did not

measure calorie and fat intake (Chiaffarino *et al.*, 1999). It is not clear whether vitamins, fiber, or phytoestrogen might be responsible for the observed effects.

Exercise

Former college athletes are noted to have a 40% lower prevalence of fibroids compared with nonathletic. It is not clear whether this difference represents the effects of exercise or lower conversion rates of androgens to estrogens due to lean Body mass.

Oral contraceptives

There is no definite relationship between oral contraceptives and the presence or growth of fibroid. One study found an increased risk of fibroids with oral contraceptives (Samadi *et al.*, 1996), but a subsequent study found no increased risk with use or duration of use (Parazzini *et al.*, 1992).

Pregnancy

Increased parity decreases the incidence and number of clinically apparent fibroid (Baird and Dunson, 2003). Fibroids share some characteristics with normal myometrium during pregnancy, including increased production of extracellular matrix and increased expression of receptors for peptide and steroid hormones. The postpatum myometrium returns to normal weight, blood flow, and cell size via apoptosis and dedifferentiation (Cesen-Cummings *et al.*, 2003).

This remodeling process may be responsible for the involution of fibroid. Another theory postulates that the vessels supplying fibroid regress during involution of the uterus depriving fibroid of their source of nutrition. Childbearing during the midreproductive years (age 25 to 29 years) provides the greatest protection against fibroid development. Pregnancies early in the reproductive years before age 25, may occur before the formation of fibroid, and pregnancies after age 30 may occur when myomasfibroids are too large to regress (Baird and Dunson. 2003;Cesen-Cummings *et al.*, 2003).

Smoking

Smoking may reduce the incidence of fibroid. A number of factors decrease bioavailability of estrogen at the target tissue; reduced conversion of androgens to estrogen secondary to inhibition of aromatase by nicotine, increased hydroxylation of estradiol, or stimulation of higher sex hormone-binding globulin.

An epidemiologic study of African-American women did not find an increased risk of fibroids among smokers, and postulated that a decrease in estrogen may be encountered by cell proliferation stimulated by components of smoke such as dioxin.

Tissue injury

Cellular injury or inflammation resulting from an environmental agent, an infection or hypoxia has been proposed as mechanisms for initiation of fibroid formation. However, no increased incidence has been found in women who have had sexually transmitted infections, an increased number of sexual partners, a younger age at first intercourse, prior intrauterine device use, or prior talc exposure. Herpes simplex virus I or II, cytomegalovirus,

Ethnicity

A large study of women screened for the presence of fibroid by self-report, medical record review, and sonography found that African-American women had a 2.9 times greater risk of having myomas than Caucasian women, and that this risk was unrelated to other known risk factors. African-American women also have fibroid present at a younger age, and have more numerous, larger, and more symptomatic fibroid (Marshall *et* a*l*., 1998). It is unclear whether these differences are genetic or due to known differences in circulating estrogen levels, estrogen metabolism diet, or environmental factors.

Hormones

Estrogens

Uterine leiomyoma growth is strictly related to estrogens and their receptors.

Several studies found that mRNA and protein expression levels as well as the content of ER-α and ER-α are higher in leiomyoma compared to those in normal myometrium (Kovacs *et* al., 2001). According to their hypothesis, estrogens may exert their growth-stimulatory effects on leiomyomas intermediated by cytokines, growth factors, or apoptosis factors. Ishikawa *et* a*l*., (2010) suggested that estrogens can maintain progesterone receptor (PR) levels, and thus progesterone through its receptor may promote leiomyoma growth. Furthermore, other authors suggested that estrogens may stimulate leiomyoma growth partially by suppressing normal p53 functions. Estrogens are able to regulate the expression growth factors by activating some signaling pathways. Estrogens up-regulate platelet derived growth factor (PDGF) expression (Barbarisi *et* al., 2001) in leiomyoma cells, while they down regulate activin and myostatin (Ciarmela *et al*., 2010) in human myometrial explants. In addition, estrogens also down regulate epidermal growth factor (EGF) expression but up-regufate the expression of EGF- R in both myometrium and leiomyoma cells. These estrogen actions are accomplished through the rapid activation of different kinds of kinases; some of them (Nierth-Simpson *et al.*, 2005) result to be increased in both immortalized uterine smooth muscle and leiomyoma cell lines under estrogen stimulation. In addition. Park and colleagues reported that estrogens may also stimulate the proliferation of leiomyoma cells by activating ATP-sensitive potassium channels *(Park et* a*l*., 2008).

Progesterone

Progesterone interacts with its receptors PR-A and PR-B playing a key role in myometrial and leiomyoma biologies (Maruo *et* al., 2010). Several studies have stressed that PR content and mRNA levels are higher in leiomyoma than those in normal myometrium . leiomyoma growth is influenced by progesterone interaction with some growth factors: it up-regulates the EGF (mitogenic) and transforming growth factor- (TGF-) β3 (bimodal action) (Arici and Sozen 2000) expression. On one hand, progesterone seems to down regulate IGF-I expression through PRB, while PRA appears to inhibit this function. Some authors hypothesized that progesterone could stimulate leiomyoma cell growth and survival through up regulating B-cell lymphoma- (Bcl-)2 protein expression and down regulating tumor necrosis factor- (TNF-) αexpression (Kurachi *et al.,* 2001 and *(*Yin *et al.,* 2007). In the same way, Yin et al. found eighteen novel PR-binding sites, one of which is Kruppel-like transcription factor 11 (KLF11) which is minimally down regulated by progesterone (Yin *et al.,* 2010).

Growth Factors

several growth factors, such as vascular endothelial growth factor (VEGF), EGF, heparin binding epidermal growth factor (HB-EGF), PDGF, IGF, TGF-a, TGF-|3, acidic fibroblast growth factor (aFGF), and basic flbroblast growth factor (bFGF), and their respective receptors have been demonstrated to play a role in leiomyoma growth (Ciarmela *et al.,* 2011). In particular, bFGF and VEGF have also been shown to promote angiogenesis in leiomyoma. EGF and PDGF seem to increase DNA synthesis and polyploidization in leiomyoma cells through transient activation of kinase pathways. PDGF also modulates the rate of cell proliferation in myometrium and leiomyoma cells (Arici and Sozen 2003; Liang *et al.,* 2006; Suo *et al.,* 2009). TGF-$\beta 3$ induces elevated expression of ECM-related genes and decreases the expression of ECM degradation-related genes (Joseph *et* al., 2010). TGF-βcan also activates kinase pathways (Mitogen-activated protein kinase (MAPK)/ Extracellular signalregulated kinase (ERK)/Smad) and thereby modulates the expression of different types genes influencing the leiomyoma growth and regression. Similarly, insulin-like growth factor (IGF) may increase cellular proliferaiion in uterine leiomyoma cells through activation of the MAPK pathway (Yu et al., 2008) and thus play a crucial role in leiomyoma cell growth, by upregulation of Bcl-2 protein expression in

leiomyoma cells. Recently, activin and myostatin have been identified in the myometrium and in leiomyoma. Additionally, several less studied factors such as parathyroid hormone related peptide, prolactin, endothelin-1, human chorionic gonadotropin (Horiuchi *et al.,* 2000), and pituitary tumor-transforming growth factor-1 have also been implicated or hypothesized in myometrial biology.

Vascular endothelial growth factor (VEGF) is an angiogenic peptide that has been shown to be critical for the growth of numerous tumors. *Chen et al* evaluated serum VEGF levels in women with uterine leiomyomas as a prospective biomarker. Expression of VEGF was increased in uterine fibroids compared with adjacent myometrium. The investigators conducted a prospective trial evaluating VEGF in 80 women before and after hysterectomy for symptomatic fibroid. The serum VEFG levels did not correlate with uterine weight, which was used as a surrogate marker of fibroid burden, or the number of fibroids. However, -serum YEFG levels declined after hysterectomy from 716.31 ± 457.99 to 581.81 ± 403.32 (P<.05). This, however, was not a novel finding, as it was previously demostrated that the uterus itself is an important source of VEGF production (Agrawal *et al.,* 2000). The investigators concluded rightly that serum VEFG levels did not predict uterine fibroid development, and it is not an effective biomarker for uterine leiomyoma (Chen *et al.,* 2005).

Cytokines and Chemokines

Many Cytokines, including tumor necrosis factor-a, erythropoietin (Suzuki *et al.,* 2011), interleukin- (IL-)l, and IL-6, have been implicated in development of uterine leiomyoma. Even chemokines and their receptors (MIP-1α, MIP-1β, RANTES, eolaxin, eotaxin-2, IL-8, CCR1, CCR3, CCR5, CXCR1, and XCR2 mRNA) have been shown to be mediators of the above mentioned process (*Mehrad et al.,* 2007; Broxmeyer, 2008). It was found that MCP-1 mRNA levels are higher in myometrium compared to leiomyoma and that estrogen and progestin decrease MCP-1 protein production, suggesting that MCP-1 may have antineoplastic activity in leiomyoma. IL-8 and IL-8 receptors type A have been identified with the elevated expression in myometrium compared to leiomyoma *(Senturk et al.,* 2001). It was described that this chemokine also up-rcgulales TGF-β1 and TGF receptor expression invitro in human term myometrium. In experimental systems, increasing carcinogen exposure tends to increase the number of tumors and their degree of malignancy. Low carcinogen exposure tends to produce benign neoplasms, whereas high exposure tends to produce both malignancies and higher numbers of tumors (Cramer *et al.,* 2007).

Diagnosis

Pelvic Examination

Clinically significant subserosal and intramural myomas can usually be diagnosed by pelvic examination based on findings of an enlarged, irregularly shaped, firm, And nontender uterus. Uterine size, as assessed by bimanual examination, correlates well with uterine size and weight at pathologic examination, even in most obese women (body mass index >30) ((Brooks *et al,* 2004). Routine sinographic examination is not necessary when the diagnosis is almost certain.

However, submucous myomas often require saline-infusion sonography, hysteroscopy, or MRI for definitive diagnosis (Brooks *et al*., 2004).

Imaging

The optical selection of patients for medical therapy, noninvasive procedures, or surgery depends on an accurate assessment of the size, number, and position of myomas. Imaging techniques available for confirming the diagnosis of myomas include sonography, saline-infusion sonography, hysteroscopy, and MRI. Imaging modalities cannot clearly distinguish between the benign uterine leiomyoma and he malignant uterine leiomyosarcoma, however, the latter is quite rare. Fast growth or unexpected growth, such as enlargement of a lesion after menopause, raise the level of suspicion that the lesion might be a sarcoma. Also, with advanced malignant lesions there may be evidence of local invasion. Biopsy is rarely performed and if performed, is rarely diagnostic. Should there be an uncertain

diagnosis after ultrasounds and MRI imaging, surgery is generally indicated (Brooks *et al*, 2004).

Treatment

Hysterectomy

Approximately 25% to50% requires treatment (Baird *et al.*, 2003). It is suggested that the symptoms may decrease the health-related quality of life, with 30% suffering symptoms severe enough to miss work, *fib*roid treatment includes medical and surgical management. In the United States of America, between 22 and 63% of women who seek medical help for symptoms related to uterine fibroids undergo surgical management. Of the women who undergo surgical treatment;

Medication aimed at shrinking the fibroid

Dostinex in a moderate and well tolerated dose has been shown to shrink fibroids effectively. Mechanism of action is unclear (Sankaran and Manyonda, 2008).

Ulipristal acetate is a synthetic selective progesterone receptor modulator which has been tested in several randomized trials with good results for the treatment of fibroids (Donnez *et al.*, 2014). Danazolis an effective treatment to shrink fibroids and control symptoms. Its use is limited by unpleasant side effects. Mechanism of actions is thought to be anti-estrogenic effects. Recent experience indicates that safety and side effect profile can be improved by more cautious dosing (Sankaran and Manyonda, 2008). Gonadotropin-releasing hormone analogs cause temporary regression of fibroids by decreasing estrogen levels. Because of the limitations and side effects of this medication it is rarely recommended other than for preoperative use to shrink the size of the fibroids and uterus before surgery. It is typically used for a maximum of 6 months or less because after longer use they could cause osteoporosis and other typically postmenopausal complications, the main side effects are transient postmenopausal symptoms.

Other alternative medications

Women undergo short-term medical treatment with hormonal agonists and antagonist (Carls et al., 2008), and a variety of treatments have been used for uterine fibroids which take advantage of their hormonal dependence. These include gonadotropin releasing hormone (GnRH) analogues such as buserelin and, goserelin, selective estrogen receptor modulators (SERM) such as raloxifene, selective progesterone receptor modulators (SPRM) such as ulipristal, and progesterone antagonists such as mifepristone (Song *et al.*, 2013). These drugs shrink the size of the fibroid and uterine volume (Lethaby *et al*., 2001) and hence have the potential to provide relief from symptoms in patients who undergo medical treatment. These drugs also provide symptomatic relief in patients waiting for surgery and enable or vaginal or laparoscopic surgery, allowing a shorter hospital stay and quicker return to normal activities compared with open surgery. Many of these drugs have a significant adverse event profile which limit the duration of administration. For example, GnRH analogues cause hypoestrogenism which leads to hot flushes and bone loss, limiting the treatment to a maximum of 3 to 6 months. There drugs are also associated with significant costs.

In many cases the fibroids will regrow after cessation of treatment, however significant benefits may persist for much longer in some cases. Several variations are possible, such as GnRH agonists with add-back regimens intended to decrease the adverse effects of estrogen deficiency. Several add-back regimes are possible, tibolone, raloxifene, progestogensalone, estrogenalone, and combined estrogens and progestogens (Sankaran and Manyonda 2008). Progesterone antagonists such as mifepristone have been tested, there is evidence that it relieves some symptoms and improves quality of life but because of adverse histological changes that have been observed in several trials it cannot be currently recommended outside of research setting (Malartic *et* al., 2008). Fibroid growth has recurred after antiprogestin treatment was stopped (Moravek *et* al., 2014). Selective progesterone receptor modulators, such as Progenta, have been under investigation.

The selective progesterone receptor modulator asoprisnilis currently tested with very promising results as a possible use as a treatment for fibroids - the hope is that will provide the advantages of progesterone antagonist without their adverse effects (Sankaran and Manyonda 2008). Aromatase inhibitors have been used experimentally to reduce fibroids. The effect is believed to be due partially by lowering systemic estrogen levels and partially by inhibiting locally overexpressed arotomase in fibroids (Sankaran and Manyonda 2008), however, fibroid growth has recurred after treatment was stopped (Moravek *et al,* 2014).

Myomectomy

Myomectomy is a surgery to remove one or more fibroids. It is usually recommended when more conservative treatment options fail for women who want fertility preserving surgery or who want to retain the uterus (Metwally *et* al., *2012).* There are three types of myomectomy:

It is a hysteroscopic myomectomy (also called transcervical resection), the fibroid can be removed by either the use of a resectoscope; an endoscopic instrument inserted through the vagina and cervix that can use high-frequency electrical cut energy to cut tissue, or a similar device.

A laparoscopic myomectomy is done through a small incision near the navel. The physician uses a laparoscope and surgical instruments to remove the fibroids. Studies have suggested that laparoscopic myomectomy leads to lower morbidity rates faster recovery than laparotomic myomectomy (Agdi and Tulandi, 2008)

A laparoscopic myomectomy (also known as an open or abdominal myomectomy) is the most invasive surgical procedure to remove fibroids. The physician makes an incision in the abdominal wall and removes the fibroids from the uterus. Laparoscopic myomectomy has less pain and shower time in hospital than open surgery *(Bhave et al.,* 2014).

Radio frequency ablation

Radiofrequency ablation is a minimally invasive treatment for fibroids (Beck and Melinda 2010). In this technique the fibroid is shrunk by inserting a needle-like device into the fibroid through the abdomen and heating it with radio-frequency (RF) electrical energy to cause necrosis of cells. The treatment is a potential option for women who have fibroids, have completed child-bearing and want to avoid a hysterectomy.

Uterine artery embolization

Uterine artery embolization (UAE): is a noninvasive, endovascular procedure effectively treating symptomatic fibroids. Using interventional radiology techniques the interventional radiologist occludes both uterine arteries, thus reducing blood supply to the fibroid. This intervention is not usually recommended when fertility should be preserved although subsequent pregnancies are usually possible. A small catheter (1 mm in diameter) is inserted into the femoral artery at the level of the groin under local anesthesia. Under imaging guidance, the interventional radiologist will enter selectively into both uterine arteries and inject small 500µm) particles that will block the blood supply to the fibroids. A patient will usually recover from the procedure within a few days. The UAE procedure should result in limited blood supply to the fibroids which should prevent them from further growth, heavy bleeding and possibly shrink them.

Studies indicate that women who undergo uterine artery embolization (UAE) as a treatment for uterine fibroids are at a higher risk for experiencing miscarriages in the future. Specifically, the risk of miscarrying was found to double when compared to women who had never undergone uterine artery embolization. When researchers compared miscarriage rates for pregnancies among different UAE when in which submucosal fibroids were excluded, miscarriages rates were even: (*Homer et al.,* 2010).

Potential biomarkers for fibroids

Biomarkers are sought to provide diagnostic as well as prognostic information. Ideally a good biomarker must be both reliable and reproducible. They must be easily measured in peripheral tissues or bodily fluids. A biomarker should be sensitive and specific; it should be cheap, and should detect a potentially morbid disease for which there is a useful intervention. The development of biomarkers for uterine leiomyomas would provide substantial cost savings, as they are easily accessible from the peripheral vasculature.

Prolactin

Prolactin is a protein hormone involved in a variety of mammalian physiologic actions such as lactogenesis. Prolactin mediates its function by interacting with type-1 cytokine receptors, and signals through Janus kinase, signal transducers, and activators of transcription (JAK/STAT) pathways (Brooks, 2012). Although isolated as a pituitary hormone, prolactin is expressed in other tissues including uterine leiomyomas (Myers *et al.,* 2002). A study found that serum prolactin in patients with uterine fibroids before myomectomy or hysterectomy was elevated (169.64±133.1 ng/mL) compared with postoperative levels (19.69 ± *9.54) (P<Q5)* and controls (Baban, 2009). The investigators considered a prolactin level *>35* ng/M L to be elevated; despite having 84% of patients with uterine leiomyomas meet this criteria, they did not evaluate any other etiologies of hyperprolactlnemia.

Total Protein

The total protein serum test measures the total amount of albumin and globulin in the blood. Values below the normal threshold usually are associated with nutritional deficiency, liver and kidney disease, or prolonged hemorrhage or anaemia. Elevated total protein values can be a marker of chronic inflammation or malignancies such as multiple myeloma. In a prospective trial examining total protein as a biomarker for uterine leiomyomas, the serum total protein level was lower in patients with uterine fibroids before they underwent hysterectomy for leiomyomas or myomectomy. The preoperative serum total protein levels were statistically significantly lower in patients with fibroids (5.56 ± 9.66 g/dL) and return to levels similar to fibroid-free controls 3 weeks after surgery (6.83 ± 0.9g/dl) (Baban, 2009). However, as patients with fibroids are predisposed to abnormal uterine bleeding and menorrhagia, it is possible that the reduced serum total protein demonstrated in patients with leiomyoma was a result of abnormal, heavier uterine bleeding versus the fibroids themselves.

Soluble Serum HLA-G

Human leukocyte antigen G (HLA-G) is a regulatory antigen of the immune sytem Expressed in the uterus and originally demonstrated in the cytotrophoblast (kovats *et* al., 1990), HLA-G has been demonstrated to be elevated in ovarian carcinoma and other cancers such as melanoma and breast carcinoma (Rebmann *et* al., 2003), in addition to peritoneal inflammatory conditions such as endometriosis. Basta *et al.* evaluated serum samples in 48 women who had under-went myomectomy of hysterectomy for symptomatic uterine leiomyomas. The controls consisted of healthy volunteers or surgical patients who had undergone diagnostic laparoscopy for unexplained infertility without peritoneal pathology. Patients with leiomyomas demonstrated statistically significantly higher HLA-G serum levels than the controls (9.01 vs. 3.31; P=.04) (Basta *et al,* 2009). However, there was significant overlap in serum values between the control patients and leiomyoma patients. In addition, no postoperative assessment was conducted for the HLA-G association with removal of fibroid tissue, preventing its current use as a biomarker for uterine leiomyoma.

Ghrelin and Obestatin

Ghrelin is a 28 amino acid peptide, secreted mainly in the stomach, which primary functions in control of energy homeostasis (Meier *et al,* 2004). To be active, ghrelin requires N-octanoylation at serine (Kojima *et al.,* 1999). Ghrelin and its receptors have been expressed in hormone-dependent tumors, uteri, and many other organs. In addition, ghrelin has been shown to be

involved in sterodogenesis and cellular leiomyomas. Obestatin originates from the ghrelin prohormone and is secreted by the stomach. In contrast to ghrelin, obestatin acts as in anocrectic hormone, has been implicated in cellular proliferation, and exhibits other proliferative effects, such as increasing phosphorylation of certain response elements and activation of growth factors.

Lactate Dehydrogenase A (LHDA)

Lactate dehydrogenase A (LDHA), which is involved in anaerobic glycolysis, converts pyruvate to lactate under anaerobic conditions (Koukourakis *et al.,* 2009). Its serum levels are often increased in cancer patients. The gene of LDHA is often up-regulated and has been linked to poor prognosis in various cancers. When evaluating 24 patients with leiomyomas compared with controls, Koukourakis *et al* demostrated that the patients with fibroids had statistically significantly higher serum LHDA levels (310 ± 81 vs. *256* ± 68; P=.05). However, this analysis was conducted along with endometrial cancer patients, and their LDHA levels were found to be almost identical with those of the patients with leiomyomas. Furthermore, the levels were similar to those of the patients with other malignant gynecologic pathologies such as ovarian cancer, making this a poor differentiator tomyoma from coexisting malignancy. In addition, LDH is a marker of leiomyoma metabolism and will be influenced by a variety of benign and malignant conditions that influence metabolic conditions, making it unusable in the diagnosis and follows-up observation of uterine leiomyoma (Koukourakis *et* a., 2009).

Hypermethylated Death-Associated Protein Kinase (DAPK)

Aberrant DNA methylation has been previously found in uterine leiomyomas when compared with matched myometrium (Navarro *et al.,* 2012). Hafner *et al.* evaluated hypermethylated death-associated protein kinase (DAPK) as a biomarkcr of uterine leiomyoma. Methylation-specific polymerase chain reaction (PCR) was used to detect DAPK methylation in 17 patients with uterine leiomyomas, and the results were confirmed by sequencing analysis of cloned PCR products. The investigators confirmed DAPK methylation in 35.5% of primary tissue and 23.8% of serum samples from patients with uterine leiomyoma. The primary aim of this study was to evaluate the amount of aberrant DNA methylation in ovarian cancer; and the examination of uterine leiomyoma was used as the comparison group of patients with gynecologic pathology. Unfortunately, the findings were neither sensitive nor specific for uterine leiomyoma.

Cancer Antigen-125

Cancer antigen 125 (CA125) is a marker of nonspecific peritoneal conditions and is not specific to ovarian malignancy. In a study of 55 patients with leiomyomas or adenomyosis, CA125 levels were 102.1 klU/L, 34.6 klU/L, and 33.1 klU/L in adenomyosis, leiomyomas, and controls, respectively. The CA125-positive rates as (defined as >50 klU/L) were 80%, 10%, and 5%, respectively. In a study of tumor markers, 92% of women with leiomyomas demonstrated elevated tumor markers such as elevated CA125 or CA19-9 (>40 TU/mL) (Juang *et al.,* 2006).

Studies have assessed CA125 for its utility in preoperative diagnosis of uterine sarcoma. In a retrospective study of 2,382 patients undergoing surgery for uterine leiomyoma 26 patients were diagnosed with sarcoma. The preoperative CA125 levels were not predictive of sarcoma. Another study assessed the potential role of preoperative serum CA125 for the differential diagnosis between uterine leiomyoma and leiomyosarcoma in 42 patients and 84 controls with benign pathology (Juang *et al.*, 2006).

Human Epididymis Protein 4 (HE4)

Human epididymis protein 4 (HE4) has been shown to be a promising biornarker in ovarian cancer, with improved sensitivity and specificity over CA125 in recognition of malignant pelvic masses. It is a protein initially isolated from epithelial cells in the human epididymis and is expressed throughout the body, including in the female reproductive organs. Moore et al. evaluated serum levels of HEA level CA125 in over 1,000 premenopausal and

postmenopausal women with benign pelvic disease. Of 61 patients with leiomyomas, only three patients (5%) had an HE4 level greater than the 95th percentile (Moore *et al.*, 2012). comparatively, 26% of patients with fibroids were found to have an elevated serum CA125. This study concluded that HE4 is elevated less frequently than in benign gynecologic diseases, including uterine leiomyomas, which provides the basis for its use as a biomarker for ovarian neoplasia (Moore *et al.*, 2012)

Proteomics

Initial work in proteomics has been performed to identify plasma proteins as biomarkers for diagnosing uterine fibroids used two-dimensional differential gel electrophoresis to identify differentially expressed proteins in the plasma of patients with and without uterine leiomyomas. The differentially expressed proteins were then identified by matrix-assisted laser ionization mass spectrometry. The results yielded 20 differentially expressed plasma proteins, the majority belonging to either coagulation or transportation groups with cytoskeleton, inflammatory cascade, and signal transduction proteins also being differentially expressed. The serum proteins with the highest differential expression ratios were actin, fibrinogen, gelsolin, and serotransferrin. Gelsolin is a regulator of actin assembly.

Gonadal Hormones and Growth Factors

There is evidence to support that gonadal hormone and growth factors are responsible for leiomyoma growth. To evaluate whether women with fibroids -demostrate higher steroid hormone and growth factor serum levels, 51 women with leiomyomas of >14 weeks' size were compared with 30 control fibroid-free patients. The levels of plasma insulin-like growth factor I (IGF-I) in women with leiomyomas during the follicular and luteal phases were almost identical to those fibroid-free women. Furthermore, estrone, estradiol, and progesterone were measured repeatedly in each group during both the follicular and luteal phases of the menstrual cycle and were similar in both groups Dawood and Khan-Dawood,

Cystatin C expression in the pre-eclamptic placenta

Pre-eclampsia is a leading cause of maternal and fetal morbidity and mortality. The condition is characterized by hypertension, proteinuria and a generalized systemic vasoconstriction (Redman and Sargent, 2005). Pre-eclampsia has been linked to a deficiency in the trophoblast invasion of the maternal spiral arteries, leading to a r poorly perfused feto-placcntal unit (Redman and Sargent, 2005; van den Brule *et al.*, 2005). Trophoblast invasion is a complex, multi-step process involving the concerted action of adhesion, degradation and migration processes. The degradation of the extracellular matrix requires specific enzymes, proteases, controlled by respective inhibitors (Redman and Sargent, 2005). The cysteine proteases (cathepsins) have been studied in implantation and placentation of various species and are believed to be important for trophoblast invasion (Salamonsen, 1999; Mason et al., 2002; Ishida *et* al., 2004). Cathepsins B and their inhibitor cystatin C have been reported to be expressed by trophoblasts and decidual macrophages in early human placentation and implantation (Divya *et al.*, *2002*; Nakanishi *et* al., 2005). Cystatin C is the strongest extracellular inhibitor of the cysteine proteases and may also have regulatory effects on other proteases *(Ray et al.*, 2003). Owing to its small size (13.3 kDa) and steady production, the serum level of cystatin C is a reliable marker for the glomerular filtration rate (GFR) in the non-pregnant setting (Grubb, 2000). The serum level of cystatin C is increased in pregnancy and further so in pre-eclampsia, closely correlated to functional and structural changes in the kidneys (Strevens *et al.*, 2002; 2003). consequently, the serum level of cystatin C has been proposed as a marker for the transition from normal pregnancy to pre-eclampsia and for the severity of pre-enclampsia (Strevens *et al.*, 2001). Increased serum levels of cystatin C in late pregnancy and preeclampsia have been explained by changes in renal handling of protein. However, increased synthesis and secretion of the protein is another posibility (Strevens *et al.*, 2001; Akbari,

2004), which would explain increased levels seen in duplex pregnancies without pre-eclampsia. Even though cystatin C was originally cloned from placental cDNA , expression of cystatin C has not been studied in placental tissue from late pregnancy or pregnancy complicated by pre-eclampsia. In the present study, cystatin C expression was analysed at the mRNA and protein level in human placental tissue from normal and pre-eclamptic pregnancies. Placental cystatin C expression was related to the time of onset and to the clinical degree of pre-eclampsia.

Cystatin C In Selected Patient Groups

Selected patient groups, whose muscle mass is either reduced or undergoes rapid changes, may benefit in particular from the development of a new marker of GFR. This is true for children and the elderly. Another target group includes patients for whom precise determination of GFR is critical, such as renal transplant recipients. It is therefore not surprising that many studies focus on these patient cohorts.

5T_±:in cystatin C in children and adolescents Particularly in children, gold standard methods for the determination of GFR such as inulin clearance are expensive, cubersome, and invasive, as they require catheterization for timed urine collection. Therefore, a surrogate marker of GFR is needed. The most commonly: used laboratory parameter to estimate GFR is serum creatinine. The limitations of serum creatinine as an ideal marker of GFR in children and adolescents are well established. Creatinine production depends on muscle mass (Vinge *et al.,* 1999), which increases with growth and pubertal development, especially in boys. Therefore, the reference range for serum creatinine increases with age until the end of puberty and has to be adjusted for gender from puberty onwards. Furthermore, the error produced by renal tubular creatinine secretion and non renal elimination is particularly important for children because of their physiologically low serum creatinine (Vinge *et* al., 1999) and low muscle mass (Vinge *et aL,* 1999).Under-recognition of renal dysfunction, especially by physicians not accustomed to the physiology of creatinine, is common (Randers *et al.,* 1999). A constant k is needed to reflect body composition (Schwartz *et al.,* 1976) and differing constants apply for gender and certain age groups (Schwartz *et* al., 1976). These formulae fail in patients with altered body composition or reduced muscle mass, such as patients with spina biflda, neuromuscular disease, anorexia nervosa, or liver cirrhosis (Brion *et al.,* 1989).

Unlike serum creatinine, the serum concentration of cystatin-C remains constant from around 1 to 50 years of age (Schwartz *et al.* 1976). Many studies established pediatric reference ranges. Upper reference values lie between 0.95 (Schwartz *et al.,* 1976)and 1.27 mg/1 (Simonsen *et al.,* 1985) for Dade Behring's particle-enhanced immunonephelometric assay (PFNIA), and around 1.38 mg/1 for DAKO's immunoturbidimetric assay (PETIA) (Bfkenkamp *et al.,* 1999). In this review the reference values for cystatin C obtained in a carefully selected population were 0.75 F 0.089 mg/l for children aged 4-19 years, 0.74 F 0.100 mg/1 for males and 0.65 F 0.085 mg/1 for females (aged 20-59 years), and 0.83 F 0.103 mg/l older individuals (greater than or equal to 60 years) (Bfkenkamp *et al.,1999).* In the first year of life, renal function matures physiologically. Accordingly, much higher cystatin-C values, up to 2.8 mg/1, were found at birth. These are subject to a rapid decline after birth reflecting maturation of kidney function (Bfkenkamp *et al.,* 1999).There appears to be no diaplacental transfer of cystatin-C (Cataldi *et al.,* 1999). Unlike serum creatinine, cystatin-C can thus be used to access the GFR of the newborn and even the fetus. Data in utcro (Cataldi *et al.,1999),* as well as postpartum (Cataldi *et al.,* 1999) indicate that serum cystatin-C is independent of gestational age facilitating its use in premature infants. Typically, studies test for the correlation of GFR and the reciprocal of surrogate markers to access the feasibility of using them as a surrogate marker. Cystatin-C as a marker of GFR was found to be independent of body composition (Woitas *et al.,* 2000). It has been shown recently that cystatin-C is the only marker of GFR that is reliable in patients with spina bifida or spinal cord injury in whom creatinine determinations are notoriously inaccurate (Pham-Huy *et al.,* 2003).

Cystatin-C in the elderly

Many of the limitations that apply to children are also valid for elderly people, especially for small patients with a low muscle mass. The limitations of serum creatine have been stressed for this population. Again, creatinine-based formulae such as Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) have been developed to overcome the problem. However, cystatin-C was shown to be a superior marker for the early detection of renal impairment.

Cystatin-C in pregnancy

Assessment of renal function in pregnancy remains a challenge. It is known that the GFR as measured by inulin clearance, increases early in pregnancy. This is thought to be secondary to increased renal reserve *(Sturgiss et* al., 1996). In an outpatient setting, creatinine clearance actually tends to go down in the third trimester (Davison *et* al., 1980), other studies suggest that the supranormal creatinine clearance remains stable throughout the later part of pregnancy (Strevens *et al.,* 2001), while Few studies have looked at Cystatin-C in pregnancy. *Cataldi et al.* found higher cystatin-C concentrations in pregnant women at term when compared to reference values obtained from healthy subjects. As altered renal function is an essential component of the pathophysiological process in preeclampsia and as early diagnosis is important, cystatin C was studied in this condition. Using receiver operating characteristic (ROC) analysis, Strevens and Wide-Swensson (Strevens *et al.,* 2001), showed a better diagnostic performance when compared to serum creatinine. Using iohexo] clearances as a gold standard GFR, same group also showed that the correlation between cystatin C and GFR was set at different levels for pregnant and nonpregnant women (Strevens *et al.,2002).* It was later shown that cystatin C rises progressively from the second to the third trimester in uneventful pregnancy (Strevens *et* al., 2002).

This observation might reflect the previous observation that the fractional clearance of substances with a molecular mass similar to that of Cystatin-C decreases during the last trimester, but may also suggest inconstant production during pregnancy. However, cystatin C was shown as marker of endotheliosis. More work is required to establish whether the measurement of cystatin-C will have a clinical role in the assessment for renal disease in pregnancy.

Diagnostic use of Cystatin C

Death and cardiovascular disease
Neurologic disorders
Renal transplants patients
Liver disease
Cancer
In pregnancy
Kidney function.

Laboratory measurement of Cystatin C

Cystain C can be measured in random sample of scrum (the fluid in blood from which the red blood cells and clotting factors have been removed) using immunoassays such nephelometry or particle- enhanced turbidimetry.

Conclusion

Cystatin C a protein encoded by the CST3 gene is mainly used as a biomarker of kidney function. Cystatin C is an endogenous marker of renal function because of its stable production rate from all nucleated cells and its almost exclusive elimination from the circulation by glomerular filtration. Uterine fibroid (myoma or leiomyoma) are benign growths of smooth muscle and connective tissue anchored in the muscular wall of the uterus. Fibroids are the most common female pelvic tumor; their etiology is unknown. Cytatin C will be a strong biomarker in fibroid to check for changes to cancer and renal function in the patients.

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