Review

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Biomarkers in Medicine

Biomarkers for diagnosis of pre-eclampsia and endometriosis

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Gynecological disorders are leading public health problems in developing countries with substantial impact on women's quality of life. Significant proportion of maternal mortality and reproductive morbidity is attributed to misdiagnosis and mismanagement of pregnancy related lethal pathological conditions and affect women's health. Timely diagnosis is necessary to prevent maternal deaths and to manage complications. Biomarker development will create a wide window of opportunity for early diagnosis. This review discusses the current status of biomarkers and recent advances in 'omics' technology for early screening of endometriosis and pre-eclampsia because of significant global bioburden associated with these disorders. This review will also give baseline data for future biomarker development strategies.

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Any biological index having the potential to be measured and which indicates defined biological end point like disease or developmental stage is known as biomarker. Biomarkers monitor wide range of responses, conditions, prognosis, progression or recurrence of disease from molecular level up to anatomical level. Biomarkers may include wide range of measurable or significant targets including cellular, biochemical, and immunological, genetic, physiological or molecular changes. Biomarkers help us acquire knowledge about effects and nature of an exposure and the liability of organisms towards the noxious impacts of that exposure. An ideal biomarker is highly sensitive, specific, noninvasive, easily accessible, robust (i.e., accurate, simple and cost-effective) and able to monitor disease progression, prognosis, and response to treatment.

Patients with pregnancy related disorders especially endometriosis and preeclampsia are at considerable risk of severe complications and death. To improve clinical outcomes rapid and appropriate diagnosis is necessary because catching the disease at an early stage provide sufficient time to mitigate the risks of diseases.

Despite much effort, the proper screening of disease through conventional diagnostic approaches is still a challenge and an extensive research in biomarker development will resolve this challenge. The discovery of an effective biomarker is one of the top research priorities in preeclampsia and endometriosis but the development of clinically approved biomarker assay needs further research. Till date, several potent biomarkers of endometriosis and pre-eclampsia have been reported, which could assist to make timely diagnosis but none of these biomarkers have approved yet.

Pre-eclampsia

Pre-eclampsia is disorder of pregnancy characterized by high blood pressure and damage to other organ systems. Pre-eclampsia is a leading cause of prenatal and maternal morbidity [1].

Table 1. The best studied biomarkers for pre-eclampsia.

Biomarker	Test characteristics for prediction
sFlt-1	Sensitivity 26–73.1% Specificity 88.5–100%
sEng	Sensitivity 18–85% Specificity 69–84.6%
PP-13	Sensitivity 79–100% Specificity 80–90%
PAPP-A	1st trimester Sensitivity (49.7–69.7%) Specificity (68.6–85.7%)
NGAL	Sensitivity 97.89% Specificity 93.55%
Insulin resistance	Sensitivity 73% Specificity 85%
SHBG	Sensitivity 85% Specificity 37.7%
Inhibin A and activin A	Sensitivity 87% Specificity 80%
Copeptin	First trimester Sensitivity 88% Specificity 81%
Uterine artery doppler	Positive likelihood ratio 9:1
Podocytes	Sensitivity 38–100% Specificity 70–100%

NGAL: Neutrophil gelatinase associated lipocalin; PAPP: Pregnancy-associated plasma protein; PP: Placental protein; sEng: Soluble endoglin; SHBG: Sex hormone-binding globulin.

It accounts for 2–10% of all pregnant women and affects many organ systems thus, causing stroke, renal and liver failure, respiratory compromise, cardiac dysfunction and coagulopathy. Pre-eclampsia is recognized after 20 weeks of gestation because of new onset of proteinuria and hypertension [2].

Biomarkers of pre-eclampsia

There is a dire need to develop novel diagnostic and predictive biomarkers of pre-eclampsia because of its high prevalence so that asymptomatic patients can easily be targeted for detection of anticipated complications. The best studied biomarkers for management of pre-eclampsia are discussed below (Table 1).

Soluble Fms-like tyrosine kinase-1

Soluble Flt-1 is an antiangiogenic form of VEGF-receptor 1 [3] that has been associated with development of pre-eclampsia. Elevated concentration of sFlt-1 has been observed in females with pre-eclampsia as compared with controls [4]. Serum level of sFlt-1 correlates with severity of disease [5] and significant decrease has been observed after delivery [4]. Upregulation of mRNA of sFlt-1 has been identified in the placenta of females with pre-eclampsia [6]. Several studies have shown the elevated level of sFlt-1 in nulliparity (that leads to pre-eclampsia) as compared with multiparous women [7]. Nulliparity is the risk factor for pre-eclampsia with an incidence rate two- to three-times higher than than multiparous pregnancies. A study suggested that epidemiological link between excess pre-eclampsia and nulliparity may occur because of changes in angiogenic profile in nulliparous women [8–10]. It has been reported that PlGF combined with sFlt-1 can efficiently predict pre-eclampsia. Several evidences indicate an increase in concentration of VEGF in pre-eclampsia affected women. VEFG and its receptors play an important role in neovascularization angiogenesis and vasculogenesis during range of pathological and physical processes that are tumorigenesis, pre-eclampsia and female reproductive cycle. Endothelial cell damage and tissue hypoxia triggers the secretion of VEGF. Changes in circulating level of VEGF may detect the pregnancies that are at high risk of developing pre-eclampsia [11].

Soluble endoglin

A transmembrane glycoprotein, endoglin consists of two splice variants endoglin L and endoglin S [12]. sEng is an extracellular domain fragment of a TGF-β1 and TGF-β3 coreceptor, which act antagonistically to TGF-β1 binding. Endoglin highly expresses on plasma membrane of endothelial and syncitiotrophoblast cells. Like sFlt-1, the onset

Table 2. Possible algorithms for pre-eclampsia prediction.

Model	Detection rate	False positivity rate
PAPP-A, PP-13, doppler PI	48% all cases of PE	10%
	68% early onset PE	5%
PAPP-A, inhibin A, PlGF, doppler PI	40% all cases of PE	10%
	100% early onset PE	10%
PAPP-A, PlGF, doppler PI, MAP	54% all cases PE	10%
	96% early onset PE	10%

MAP: Mean arterial pressure; PAPP: Pregnancy-associated plasma protein; PE: Pre-eclampsia; PP: Placental protein.

of the symptomatic phase of pre-eclampsia is followed by the appearance of circulating sEng. sEng inhibits tube cell formation and endothelial cell proliferation. Recent study revealed that increased concentration of sEng in serum correlates with severity of pre-eclampsia [13] because serum level of sEng remains stable during whole gestation period in normal pregnancy whereas, elevates during second trimester in women affected with pre-eclampsia [12]. Therefore, it is an effective biomarker for screening of pre-eclampsia.

Placental protein 13 & PlGF

PP13 is 32 kDa dimeric protein. It was first isolated from placenta specifically by syncytiotrophoblast [14]. It consists of carbohydrate binding domain where proteins actin-β and annexin-II bind to play an active role in maternal artery remodeling and placentation, respectively [15]. In normal pregnancy the serum level of PP13 increases whereas, abnormal decrease in concentration of PP13 has been observed in women with pre-eclampsia [16]. Measurement of PP13 during first trimester may act as potent biomarker for prediction of pre-eclampsia [13]. Maternal serum levels of sFlt-1, PP13 and FSLT3 predict late-onset pre-eclampsia [17]. Rădulescu *et al.* compared the serum level of soluble markers sFlt-1, IL-6, IL-16 and PlGF during the second and third trimester of pregnancy. The findings of study revealed PlGF as the best predictor for pre-eclampsia with a sensitivity of 100% at a concentration threshold of 120.16 pg/ml [18,19]. Likewise, another study suggested that serum concentration of PlGF was decreased and activin A and inhibin A was increased in early second trimester in women who developed pre-eclampsia [20]. Another study suggests that sFlt1:PlGF ratio may serve as best diagnostic biomarker for pre-eclampsia during the second trimester of pregnancy [21].

Pregnancy associated plasma protein-A

Placental trophoblasts secretes pregnancy associated plasma protein-A (PAPP-A) that is a protease consisting of 1628 amino acid [13]. PAPP-A regulates fetal growth [22]. A study revealed that concentration of PAPP-A was considerably decreased during early onset pre-eclampsia whereas, level of PAPP-A in the late onset pre-eclampsia was equal to control group. Therefore, PAPP-A may play an important role in preliminary examination of pre-eclampsia [23]. Kalousová *et al.*, summarize the possible algorithms for pre-eclampsia prediction during 11–13 weeks of gestation (Table 2) [24].

Neutrophil gelatinase associated lopicalin

NGAL is a protein that is 25 kDa in size. Its presence was first identified in human neutrophils as matrix proteins of specific granules. Increased concentration has been reported in neoplastic conditions, renal disorders, cardiovascular disorders, infections and inflammation [25]. A study revealed that concentration of NGAL was increased during the second trimester of pregnancy in women with pre-eclampsia as compared with control group [26]. Serum level of NGAL and its positive correlation with proteinuria and with diastolic and systolic blood pressure makes it potent biomarker for timely diagnosis of pre-eclampsia.

Insulin resistance

Insulin resistance has been associated with pre-eclampsia. Sex-hormone-binding globulin (SHBG) – a glycoprotein produced by the liver acts as marker of insulin resistance because it binds circulating estrogens and results in inhibition of T. Hepatic SHBG production by insulin. The reduction in SHBG levels is a marker of insulin resistance and hyperinsulinemia. The level of human placental lactogen (hormone responsible for insulin resistance during normal pregnancy) is reduced in pre-eclampsia. Several evidences suggest that women with pre-eclampsia

experience an increase in insulin resistance specifically during second and third trimesters compared with normal pregnancy. Some novel researches support this finding based on increased level of inositol phosphoglycan P-type (P-IPG) in women with pre-eclampsia. P-IPG is a second messenger of insulin that increases insulin resistance and metabolic effects of insulin. Insulin may help in clinical practice to monitor progression of pre-eclampsia [27].

Sex hormone-binding globulin

SHBG secreted by liver is a glycoprotein which binds with circulating testosterone and estrogen. Several studies indicate significant decrease in concentration of sex-hormone-binding globulin in pre-eclampsia affected women compared with controls [28]. Insulin inhibits the production of SHBG in liver cells thus, decreased SHBG level may acts as marker of hyperinsulinemia. The level of SHBG is increased during first and second trimesters specifically during reaching climax during 24 weeks. Thus, SHBG is considered as reliable marker for insulin resistance and diabetes. Some researchers reported no association between pre-eclampsia and SHBG whereas, some suggested complex relationship. According to Rehmanian *et al.*, independent of IR, high blood SHBG is associated with reduction of the odds of pre-eclampsia [29].

Inhibin A & activin A

Glycoproteins inhibin A and activin A has been reported as biomarkers of pre-eclampsia. Both belongs to transforming growth factor β family and are largely secreted by fetoplacantal unit during pregnancy. The serum level of both hormones elevates during third trimester of normal pregnancy but tenfold increase is observed in women with severe pre-eclampsia.

Apolipoprotein E

Pre-eclampsia is associated with serum level of ApoE and polymorphisms of ApoE gene. A study demonstrated that women with pre-eclampsia experience higher incidence of ApoE e2 allele case compared with controls [30]. However, its role as biomarker of pre-eclampsia is still uncertain.

Copeptin

A recent study demonstrated that copeptin protein that is a byproduct of arginine vasopressin can detect pre-eclampsia during first 1.5 months of pregnancy [31].

Uterine artery doppler

Several studies have suggested uterine artery doppler velocimetry as a best screening test to detect pre-eclampsia. However, according to recent evidences, the use of doppler ultrasonography is more effective in combination with angiogenic biomarkers [32].

Podocytes

Several studies associate the clinical features of pre-eclampsia with podocyte dysregulation. Ermina and colleagues suggested that deletion of one of VEGF from podocyte of mice led to development of pathological conditions in mice kidney [33]. Human-based study indicated a dominant reduction of podocyte specific protein expression in the kidneys of women with pre-eclampsia [34]. Garovic and colleagues demonstrated that urinary podocyte excretion occurred in all women affected with pre-eclampsia [35]. However, research is still underway to develop podocytes as diagnostic or prognostic markers recent evidence suggested showed contrasting results that podocyturia may occur at a low level during normal pregnancy.

Proteomics

The field of proteomics provides powerful tools that assist in discovery of disease markers based on rapid identification as well as quantification of proteins. This field will have profound implications on the clinical management and diagnosis of pre-eclampsia through the discovery of novel biomarkers. The total content of proteins present in any biological fluid (urine, blood or amniotic fluid) or biological compartment (organelle, cell and organism) is proteomics. Altered protein expression can be used in the discovery of biomarkers. The research related to urinary proteomics led to identification of pre-eclampsia biomarkers such as fragments of albumin and SERPINA1. Serine protease SERPINA1 is synthesized by many cell types specifically trophoblasts [36]. Proteomic profile consisting of fragments of albumin and SERPINA1 has been observed in the urine of pre-eclampsia affected females [37]. Likewise, other study has identified about 31 proteins that are specifically expressed in pre-eclampsia patients [38].

Metabolomics

Metabolomics deals with characterization of metabolites or small molecules found in biological systems [39]. Odibo *et al.*, suggested the effective role of metabolomics for diagnosis of pre-eclampsia during first trimester. Four metabolites (phenylalanine, alanine, glutamate, and hydroxyhexanoylcarnitine) were found to be significantly higher in pre-eclampsia affected females compared with normal healthy controls [40]. However, the field of metabolomics is still in infancy and need further thorough research.

Other novel biomarkes

The identification of novel noncoding RNAs, snoRNAs and mRNAs specifically Kell blood group determinants, urothelial cancer associated 1, miRNA-22, miR-517-5p, miR-518b and miR-520h and the roles of PRG2, mis-expressed by various trophoblast subpopulations in severe pre-eclampsia offers hope for the development of new biomarkers. In severe pre-eclampsia number of cajal body foci were found to be double in cytotrophoblasts. The severity of PE can also be measured by higher level of angiogenesis, antiangiogenesis and cell damage in patients who develop HELLP syndrome. Recent study have demonstrated that RBP-4 can also serve as biomarker of pre-eclampsia because concentration of RBP4 concentration gets lower in pregnant women with severe pre-eclampsia than those with healthy pregnancy [41] whereas, another recent study has shown the upregulation of RBP4 and downregulation of PAPP-A in early pregnancy of pre-eclampsia patients as compared with normal pregnancies. The comparison of maternal and cord blood levels among pre-eclampsic pregnant women and normotensive pregnant women showed increase in the level of lipid profile (namely, total cholesterol, triglycerides, LDL-C, VLDL-C and HDL-C), heme oxygenase 1, TSH, folic acid and homocysteine and decrease in the level of endoglin, IGF-I, cholinesterase, IGF-I, blood vitamin B12 and Apo A-I and Apo B l [42]. SPGF, uterine artery pulsatility index and mean arterial pressure (MAP) may form the basis of screening for pre-eclampsia. Another biomarker for renal injury in pre-eclampsia is Urine KIM-1 [43]. Urinary nephrin may also be a useful biomarker of pre-eclampsia because of its observed higher concentration in pregnancy with pre-eclampsia as compared with normal pregnancy [44]. Some other recent studies have shown the differential expression of several proteins such as myeloid cell nuclear differentiation antigen, vitamin D-binding protein, keratin, Type I cytoskeletal 9 (K1C9), α-1-antitrypsin , transferrin, CD5 antigen-like molecule, zinc-α-2-glycoprotein, haptoglobin, β-2-glycoprotein 1 (APOH), vitronectin, α-2-HS-glycoprotein (FETUA) and complement factor B in the plasma of women suffering from pre-eclampsia [45]. The increased urinary concentration of MMP-2 at 12 and 16 weeks of gestation predicts an increased risk of pre-eclampsia [46]. Amniotic fluid compositional changes such as uric acid, potassium and cysteine to methionine ratio levels may help in diagnosis of pre-eclampsia. Inflammation biomarkers specifically cytokines; IL-1β, -6 and -10, CRP and TNF-α and oxidative stress biomarkers such as 8-hydroxydeoxyguanosine and 8-isoprostane may also help in the detection of pre-eclampsia at early stages [47]. Some of the immune biomarkers of pre-eclampsia are IL-6, IL-4, IL-5, IL-12, IL-10, IL-8, IL-1-β, TNF-α and beta, RANTES, IFN-γ, brain-derived neurotrophic factor and TGF-β [48,49]. The value of hematocrit-albumin >12.65 may help in the auxiliary diagnosis of pre-eclampsia and eclampsia in hypertensive disorders of pregnancy [1]. Some differentially expressed genes and rSNPs in pre-eclampsic women are rs10423795 in the *LHB* gene; rs3771787 in the *HK2* gene; rs72959687 in the *INHA* gene; rs12678229, rs2227262 and rs3802252 in the *NDRG1* gene; rs34845949 in the *SASH1* gene and rs66707428 in the *PPP1R12C* gene [50]. Progranulin and soluble endoglin are putative new biomarker for an early detection of intrauterine growth restriction and pre-eclampsia in women [51]. Cereberal biomarkers for example, NSE and S100B were observed elevated 1 year postpartum in women who had pre-eclampsia in contrast to women with previous normal pregnancies [52]. Oxidative stress markers may also predict pre-eclampsia for example, activity of catalase, vitamin C, thiol groups and δ-ALA-D (delta-aminolevulinate dehydratase) were found to be lower in pregnant women with pre-eclampsia whereas, thiobarbituric acid-reactive species was higher in pregnant women with pre-eclampsia as compared with healthy pregnant women [53].

Endometriosis

Endometriosis is an estrogen-dependent benign inflammatory disorder associated with dysmenorrhoea, intermenstrual bleeding, dyspareunia, pelvic pain and infertility. It is the leading cause of infertility in USA because 10 million women are known to have affected with this disorder currently. The 2–10% and 35–50% prevalence have been reported in reproductive age women and women with unexplained infertility, respectively. Endometriosis can have negative effects on the physiological development of pregnancy. Pregnant women may also experience changes of endometriotic cysts that are rapidly growing and abundantly vascularized intraluminal vegetations and ovarian

Table 3. The best studied biomarkers for endometriosis.

Biomarker		Test characteristics for prediction
CA-125 + prolactin		Sensitivity 77% Specificity 88%
Glycoproteins	Follistatin	Sensitivity 92% Specificity 96%
	Zn-α-2-glycoprtoein	Sensitivity 69.4% Specificity 100%
	Glycodelin	Sensitivity 78.4% Specificity 82.1%
Cytokines	Serum IL-6	Sensitivity 100% Specificity 100%
	Serum IL-8	Sensitivity 90% Specificity 92%
	TNF-α	Sensitivity 95% Specificity 86.2%
	Serum CRP	Sensitivity 85% Specificity 93.7%
miRNA		Sensitivity 93.22% Specificity 96.00% [58]
ICAM-1		Sensitivity 58.3% Specificity 60.0%
Circulating cell-free DNA		Sensitivity 70% Specificity 87%
Autoantibodies		Sensitivity 83% Specificity 79%

CA-125: Cancer antigen-125; CRP: C-reactive protein; ICAM-1: Intercellular cell adhesion molecule-1.

endometrioma transformation. Some evidences reveal that complications such as small for gestational age babies, preterm births, miscarriages, cesarean delivery, gestational diabetes mellitus, placenta praevia, obstetric hemorrhages and hypertensive disorders [54]. Hadfield *et al.*, reported that no association exists between endometriosis and pre-eclampsia [55] in contrast to the findings of Broson *et al.*, who reported that endometriosis is associated with decreased risk of pre-eclampsia [56].

Biomarkers of endometriosis

Previous studies have focused on the association of endometriosis with adhesion molecules, inflammatory and noninflammatory cytokines, angiogenic and growth factors, glycoproteins – among others, however, not a single biomarker has been validated as effective screening test for endometriosis.

Study analyzing 28 biomarkers revealed that only four to five biomarkers (glycodelin, VEGF, CA-125, sICAM-1) enabled the detection of endometriosis with 63–81% sensitivity and 81–90% specificity [57]. Discussed below are the best studied biomarkers of endometriosis (Table 3).

Cancer antigen-125

Cancer antigen-125 (CA-125)-glycoprotein antigen is expressed in in nonmalignant pelvic conditions for example, fibroids, endometriosis, pregnancy and pelvic inflammatory disease as well as epithelial ovarian cancer. The use of CA-125 as biomarker of endometriosis has been extensively studied. Number of evidences correlate CA-125 with severity and diagnosis of diseases especially endometriosis and endometriotic ovarian cyst [59] because CA-125 is not specific for endometriosis, it acts as tumor marker in cases of ovarian cysts as well. Although, some evidences suggest that CA-125 lacks sensitivity and specificity even than CA-125 is the only biomarker that has been translated to the clinic as a biochemical marker to diagnose endometriosis [60]. However, endometriosis was easily diagnosed when CA-125 and prolactin were assessed together.

Glycoproteins

Serum proteins related to symptoms of pre-eclampsia such as hypertriacylglycerolemia, low-grade inflammation and obesity would serve as new markers in clinical practice. Several different proteins that increase or decrease to certain level in pre-eclampsia are IGF-binding protein-1, IGF-1, α fetoprotein, sEng, human chorionic go-

nadotrophin, PAPP-A, PP13, sFlt-1, sVEGFR-1, VEGF and PlGF. Pre-eclampsia is characterized by dysfunctional angiogenic pathway and coagulation system and histidine rich glycoprotein is a protein that interacts with both these biological systems. Serum level of histidine rich glycoprotein might act as a marker for identification of later onset of pre-eclampsia in gestational week 10. The serum level of follistatin elevates in women with endometriosis [61] and exhibits good specificity and sensitivity. Signorile and Baldi introduced Zn-α-2-glycoprtoein as potent biomarker of endometriosis with 69.4% sensitivity and 100% specificity [62]. Increased concentration of glycodelin that has been observed in patients with endometriosis favors its use as potent biomarker of endometriosis with 78.4% sensitivity and 82.1% specificity [63].

Cytokines

The use of immunological and inflammatory cytokines as biomarkers of endometriosis has been studied extensively. Number of cytokines such as MCP-1, TNF-α, interferon-γ (IFN-γ), IL-1, IL-6, and IL-8 has been examined in search for noninvasive screening of endometriosis [61]. Significant increase in IL-4, YKL-40, C-reactive protein (CRP), and co-peptin has been observed in patients with endometriosis. Likewise, the concentration of MCP-1, IL-8, and RANTES was found to be higher in peripheral blood of patients with endometriosis. Mihalyi *et al* reported that panel consisting of luteal plasma levels of CA-125, TNF-α, and IL-8, distinguished endometriosis patients from normal control with 71.1% specificity and 89.7% sensitivity. IL-8 which is an autocrine growth factor in the endometrium is the potential candidate for biomarker discovery [64].

miRNA

Fassbender *et al.*, suggested the use of miRNAs in peripheral blood as effective biomarkers of endometriosis [65]. Increased plasma levels of miR-16, miR-191 and miR-195 [66] and reduced levels of miR-22, miR-20a and miR-17-5p have been observed in women affected with endometriosis [67]. Likewise, another study revealed an increase in serum concentration of miR-122, miR-199a and decrease in miR-9* miR-542-3p, miR-141* and miR-145*in endometriosis affected women [58]. Serum let-7 family miRNA family have also shown dysregulation in endometriosis [68]. This overexpression of several miRNAs peritoneal endometriotic lesions compared with healthy surrounding tissues will form the basis of development of biomarker for endometriosis [69]

Cell adhesion & invasion

Concentration of soluble intercellular cell adhesion molecule-1 (sICAM-1) elevates during early stages of endometriosis and decreases at late stages [61]. Likewise, increase in level of MMPs [70] specifically MMP-2 [71] and MMP-9 [72] have been observed in endometriosis affected patients compared with normal individuals.

Cell populations

Although none of cell population such as macrophages/monocytes, T cells, B cells, polymorphonuclear neutrophils and natural killer cells has been proved as biomarker of endometriosis however, recent evidence revealed decrease in serum level of $CD25^{high}$ forkhead box 3^{+} ($FOXP3^{+}$) subset of $CD4^{+}$ regulatory T cells in endometriosis patients compared with normal healthy females [73].

Circulating cell-free nucleic acids

Circulating cell-free (ccf) nucleic acids in plasma and serum may form the basis of noninvasive monitoring of variety of benign and malignant proliferations and inflammatory conditions. Zachariah *et al.*, reported an increase in concentration of ccf nuclear DNA in endometriosis however, use of this ccf DNA needs further research [74].

Oxidative stress

Several studies exhibited significant decrease in serum level of plasma superoxide dismutase [75], high density lipoproteins, paroxonase (PON-I) [76] and increase in concentration of low-density lipoprotein, total cholesterol, triglycerides, lipid peroxidises [76], heat shock protein 70b′ (HSP70b′) [77], 25-hydroxycholesterol [78] and vitamin E [75]. Lower level of serum total thiol, native thiol and higher level of catalase levels observed in endometriotic patients make oxidative stress biomarkers an efficient tool to monitor the disease's progress during the treatment [79].

Autoantibodies

In endometriosis, autoantibodies response to endometrial antigens such as carbonic anhydrase, transferrin and α(2)-heremans schmidt glycoprotein. Use of antiendometrial antibodies as biomarker of endometriosis exhibited

promising results because total count of antiendometrial antibodies was found to be higher in endometriosis patients compared with controls. Likewise, specific antibodies against cardiolipin, lipid peroxide modified rabbit serum albumin, transferrin, carbonic anhydrase, laminin-I, α2-HS glycoprotein, malondialdehyde-modified low-density lipoprotein and copper oxidized low-density lipoprotein have shown promise as effective biomarkers of endometriosis [61]. Likewise, an increased concentration of antisyntaxin 5 autoantibodies [80] and serum anti-PDIK1L [81] in endometriosis patients have also been reported. Autoantibodies against IGF-2, mRNA-binding protein 1 (IMP1) [82] and epitopes of stomatin-like protein 2, tropomodulin 3 (TMOD3) and tropomyosin 3 (TPM3) has been found to be significantly higher in endometriosis patients [83].

Angiogenic factors

In angiogenesis, angiogenic factors activate proteases derived from vascular endothelial cells and dissolve basement membrane, migrate and proliferate endothelial cells and form capillary tube. Angiogenic factors involved in this process are: IL-8, estradiol, angiogenin, proliferin, pleiotropin, tumor necrosis factor, HGF, platelet-derived endothelial cell growth factor, platelet-derived growth factor, transforming growth factor α and β, epidermal growth factor, placenta growth factor, VEGF and basic FGF. Increased concentration of VEGF has been observed in patients of endometriosis [84] however, its use as biomarker is still unclear because of contrasting results obtained from another study [85]. Serum concentration of PEDF was decreased [86] whereas, HGF [87], FGF-2, soluble Flt-I (VEGFR-1), and angiogenin was increased in women with endometriosis [61].

Proteomics

A lot of research regarding proteome fingerprint technology has been done to develop biomarker for screening of endometriosis. Proteomic fingerprint model with three peptide peaks exhibiting 95% specificity and 91.4% sensitivity has been observed in 126 endometriosis affected patients compared with 120 normal controls [88]. Another combination of five peptide peaks that identified endometriosis with 84% specificity and 88% sensitivity has also been reported [89]. Proteomic technologies may form the basis of development of an effective biomarker for endometriosis because of promising results obtained in variety of researches.

Metabolomics

Studies regarding metabolome of patients are enabling the scientists to evaluate the progression of disease. Significant decrease in stearic acid was observed in endometriosis patients [90]. Another study has suggested the association of endometriosis with increased levels of phosphatidylcholines and sphingomyelins providing 84.3% specificity and 90.0% sensitivity for screening of endometriosis [91]. Dutta *et al.*, reported that concentration of 3-hydroxybutyrate, lactate, glycerophosphatidylcholine, L-alanine, L-leucine, L-lysine, L-threonine, L-valine, succinic acid and 2-hydroxybutyrate were increased whereas, concentration of L-isoleucine, glucose and L-arginine was decreased in endometriosis affected females [92]. More research on metabolomics and metabonomics is required to develop potent biomarker for noninvasive diagnosis of endometriosis.

Other biomarkers

High-throughput molecular studies have opened an avenue to the rational discovery of molecules that are overexpressed in women with endometriosis. mRNA expression levels for surviving, VEGF and CA-125 are peripheral blood markers that act as diagnostic tools for endometriosis [93]. Munros *et al.*, reported an increased level of total circulating microparticle levels in patients with deep infiltrating endometriosis [94]. A recently published Cochrane review evaluated 122 serum biomarkers of endometriosis in more than 15,000 subjects and found out CA-125 as the most potent biomarker produced by endometrial and mesothelial cells in response to inflammation [95]. Likewise, 214 proteins that were differentially expressed in ovarian endometrioma versus eutopic endometrium from the same patients have also been reported [96]. Grande *et al*, analyzed the cervical mucus samples of endometriosis patients and detected large number of proteins that were differentially expressed. Nine proteins including some involved in protection against oxidative stress (HSPB1) and local innate immunity (CRISP-3 and Pglyrp1) were reduced and six proteins were increased in endometriosis [97]. Eutopic endometrium is an important source of potential diagnostic biomarkers because of differential expression levels of noncoding RNA in tissue as well as in blood [98]. Different SNPs in six genetic loci including 7p15.2, VEZT, WNT4, CDKN2B-AS1, GREB1 and ID4 as well as SNPs located on the locus of VEZT and CDKN2B-AS1 may also serve as biomarkers for endometriosis. The development and validation of these biomarkers in clinics will facilitate the early diagnosis of endometriosis.

Future perspective & conclusion

In last decades, research in endometriosis has identified variety of markers associated with genetic, polymorphisms, immunology, adhesion, oxidative stress, circulating cells, miRNAs and hormonal receptors. But none of these are useful for clinical practice furthermore, additional potent biomarkers have been reported with the advent of 'omics' that help scientific community detect myriad of genetic and molecular features at once.

Proteomic and transcriptomic analysis of endometrial fluid and blood have been applied to monitor the severity of endometriosis. New markers are on the horizon with the advent of omics technology.

From a diagnostic standpoint, proangiogenic factors such as VEGF, PIGF, NGAL, sEng, sFlt-1 have shown to be effective biomarkers of pre-eclampsia. Likewise, several cytokines (MCP-1, TNF-α, IFN-γ, IL-1, IL-6 and IL-8), glycoproteins (follistatin, glycodelin A), miRNA, autoantibodies and angiogenesis factors (VEGF, PEDF, HGF, FGF-2) have been found efficacious for the screening of endometriosis.

Despite of promising results obtained through these emerging new biomarkers, extensive clinical research is still needed for validation. None of these biomarkers fulfill the WHO criteria for biomarker selection to diagnose pre-eclampsia and endometriosis. Biomarker research in both these disorders still lack reproducible data with high specificity and sensitivity. Metabolomics and proteomics offer new opportunities and potential advantages compared with conventional and classic diagnostic approaches. Scientific community must explore the challenges hindering the validation of candidate biomarkers for endometriosis for pre-eclampsia.

Executive summary

- Gynecological disorders are leading public health problems in developing countries with substantial impact on women's quality of life.
- Timely diagnosis is necessary to prevent maternal deaths and to manage complications. Biomarker development will create a wide window of opportunity for early diagnosis.
- This review discusses the current status of biomarkers and recent advances in 'omics' technology for early screening of endometriosis and pre-eclampsia because of significant global bioburden associated with these disorders.

Pre-eclampsia

- From a diagnostic standpoint, proangiogenic factors such as VEGF, PIGF, neutrophil gelatinase associated lipocalin (NGAL), soluble endoglin (sEng) and soluble Fms-like tyrosine kinase-1 (sFlt-1) have shown to be effective biomarkers of pre-eclampsia.

Endometriosis

- Likewise, several cytokines (MCP-1, TNF-α, IFN-γ, IL-1, IL-6 and IL-8), glycoproteins (follistatin, glycodelin A), miRNA, autoantibodies and angiogenesis factors (VEGF, PEDF, HGF, FGF-2) have been found efficacious for the screening of endometriosis.

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