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Cardiovascular Diseases Associated with Pregnancy: Early Assessment Using Non-Invasive MicroRNA Profiling

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Abstract

In some cases pregnancies are associated with severe cases of cardiovascular diseases (CVDs). The early detection and proper treatment of CVDs during maternity is detrimental to the health outcome and wellbeing of both mother and child. Unfortunately, both the detection rate and assessment of CVDs during pregnancies are unsatisfactory.

Currently, the messenger RNA (mRNA) regulators called microRNAs (miRNAs) are being extensively profiled for use as clinical CVDs biomarkers due to their specific tissue and disease expression signature profiles. The identification and development of reliable biomarkers for early clinical assessment of CVDs during pregnancy could allow the detection of sub-clinical cardiac injury risk in vulnerable pregnant patients before irreversible damage occurs. CVDs specific miRNA biomarkers could provide the clinicians with a valuable tool to allow prognosis of patients at risk of cardiovascular injury and the introduction of therapy and intervention in order to increase health outcome and survival rate of both the mother and child.

Cardiac diseases during pregnancy

Cardiac diseases account for 2-4 % of maternal death associated with pregnancy and the maternal mortality rate due to cardiac diseases has been reported to be 2.31 per 100,000 maternities in United Kingdom (UK) in 2006-2008 [5]. The most frequent form of cardiac disease in pregnant women is congenital heart condition, which is characterised by tiredness and fatigue, shortness of breath, dizziness, rapid heartbeat and/or chest pain [6].

Classification	Symptoms and limitations
Class I	No symptoms from ordinary activities
	No limitation of activities
Class II	Comfortable with rest or mild exertion
	Fatigue, palpitation, dyspnea and/or anginal pain with more than ordinary physical activity
	Slight/mild limitation of activity
Class III	Comfortable with rest
	Fatigue, palpitation, dyspnea and/or anginal pain with less than ordinary physical activity
	Marked limitation of activity
Class IV	Discomfort is increased if any physical activity is undertaken
	Even at rest symptoms of cardiac insufficiency or of anginal syndrome may be present
	Any physical activity brings on discomfort and symptoms occur at rest
Modified from American Heart Association website www.heart.org (2015)	

Table 1: New York Heart Association: Functional Classification of Heart Diseases.

As the blood volume is increased during pregnancy it is expected to have some of this symptoms, making it difficult to distinguish when this due to an impaired heart. A physical examination will determine if any cardiac abnormalities are present. In case a cardiac disease is detected the damage will be localised and specified (eg. valve, cardiac muscle, endocardium or arrhythmia) and whether it is congenital or acquired will be determined. The severity of the injury will be assessed using the New York Heart Association (NYHA) classification of heart disease (American Heart Association guidelines: www.heart.org) (Table 1). Fortunately, the majority of heart diseases (>90%) observed during pregnancy are class I and II and are therefore not linked with any substantial symptoms or risks involved for nor mother or child. However, some pregnancy cases involve class III and IV heart diseases and are associated with more complications and are usually diagnosed prior to pregnancy (Table 2). Peripartum cardiomyopathy (PPCM) is a very severe life-threatening idiopathic form of heart failure due to left ventricular systolic dysfunction [7]. PPCM is observed in the last month of pregnancy or within 5 months after delivery and is quite rare as PPCM affects approximately 1 in 2,000 pregnancies in UK [8] and accounts for about 1 in 6 deaths linked to cardiac disease during pregnancies [9]. The incidence of PPCM is much higher in developing nations, such as Haiti (1 in 300) and South Africa (1 in 1,000) [10-12]. A report by Cantwell et al. 2011, showed that a total of 53 pregnant women died due to cardiac maternal deaths during 2006-2008 in UK, and half of these women were never assessed by electrocardiograms or cardiac injury biomarkers [5], highlighting that there were critical lessons to be learnt from their health management.

Risk of maternal mortality	Mortality rate	Cardiac lesion types
Low	(<1%)	Most Class I or II lesions of NYHA
		Patent ductus arteriosus
		Pulmonic/ tricuspid lesions Septal defects
Moderate	(5%-15%)	Most Class III or IV NYHA lesions, especially mitral stenosis
		Tetralogy of Fallot Aortic stenosis
		History of Myocardial Infarction
		Marfan syndrome with normal aorta
High	(25%-50%)	Eisenmenger's syndrome
		Marfan syndrome with abnormal aortic root
		Peripartum cardiomyopathy
		Pulmonary hypertension
Modified from Handbook of Critical Care Obstetrics (by S.L. Clark, J.P. Phelan, G. Hankins & D.Cotton), 1st Ed, Wiley-Blackwell (1994).		

Table 2: Risk of maternal mortality and cardiac lesion types observed.

Potential biomarkers for cardiac injury assessment: miRNAs

The short (~22 nucleotides), single-stranded, non-coding RNA molecules called miRNAs play an important role in post-transcriptional gene regulation, as they induce mRNA translation repression or degradation [13]. So far >1,000 miRNAs have been detected in the human genome (**www.miRBase.org**). One miRNA can target and regulate several mRNAs, and furthermore, one mRNA can be targeted and regulated by a diverse set of miRNAs [14]. The key functions of miRNAs include differentiation, proliferation, apoptosis, metabolic homeostasis, tumorigenesis and DNA methylation [15-17]. Determining the miRNA profile can provide vital information on the physiological and pathological state [17].

Cardiac diseases and miRNA expression

As pointed out by Yang et al. 2008, miRNAs have different expression signature under different pathological conditions [18]. A comparison of various studies investigating miRNA profiles in ischemic myocardium and hypertrophic hearts affirmed that the miRNA expression went in the opposite directions between these two pathological conditions. During cardiac hypertrophy miR-208, miR-214, miR-320 and miR-351 are upregulated, while the same miRNAs are downregulated in myocardial infarction. During myocardial infarction miR-1, miR-29a, miR-30 and miR-181b are upregulated, while the opposite effect is observed during cardiac hypertrophy. In addition, cardiac dysfunction has been associated with an altered expression of miR-21, miR-27b, miR-29, miR-126 and miR-195 [19-22], while an altered expression of miR-1, miR-133a, miR-133b, miR-208a and miR-499-5p is observed during acute myocardial infarction [23-26]. Arrhythmias have showed an altered expression of miR-1, miR-133 and miR-208a [27-29], while fibrosis is associated with alteration of miR-21 and miR-29 [18,22].

Cardiac diseases during pregnancy and miRNA profiling as a screening tool

As a result of limited sensitivity and specificity and the high costs and availability of current techniques for assessing cardiac injury (i.e. imaging techniques such as Doppler echocardiography, endomyocardial biopsies and serum protein biomarkers) there is an urgent need for developing a new non-invasive and cost-effective diagnostic tool for early detection of cardiac injury [30-32]. Investigating the miRNA expression profiles of pregnant women in the

risk zone for cardiac diseases may be useful for diagnosis and prediction of pregnancy-related cardiac diseases [33]. Some studies have looked at the miRNA expression profiles linked with CVDs and preeclampsia in placental tissue [34,35]; however, it is more beneficial to sample the maternal circulation for early detection of cardiac injury, by potentially implementing miRNAs as biomarkers in clinical assessment routines. A study by Hromadnikova et al. 2013, showed that upregulation of miR-516-5p, miR-517, miR-520a, miR-525, and miR-526a is a characteristic phenomenon of established preeclampsia [36]. Furthermore, the downstream-mediator of 16-kDa N-terminal prolactin fragment miR-146a was elevated in the plasma and hearts of PPCM patients, but not in patients with dilated cardiomyopathy [37,38]. Studies have shown that placental miRNAs are released into the maternal circulation [14] and these miRNAs may have an important role in development of CVDs in the mother and should be examined carefully.

Conclusion

Novel examination into miRNA expression profiles of pregnant women prone to develop or with known profiles of cardiac diseases will give a valuable screening tool to detect cardiac injury risk at an early stage and ensuring that the clinicians can tackle the symptoms before an irreversible stage is reached, thus improving the outcome for both mother and child.

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