Detecting peripartum cardiomyopathy

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Peripartum cardiomyopathy is a complication that can affect women in the final stages of pregnancy and up to six months after birth. This heart disease is very rare, affecting one pregnant woman or young mother in 3,500 in our country. The disease is much more common in Africa and reaches record levels in Haiti where it affects one in 300 women. What is at issue is a fragment of prolactin, an hormone involved in the growth of mammary glands and the stimulation of milk production.

A study by Ingrid Struman's team, carried out in collaboration with German and South-African researchers at the University of Liege has revealed a biomarker, a microRNA which makes it possible to distinguish this condition from other cardiac diseases that cause heart failure. The research also explains how the disease develops: the prolactin fragment destroys the blood vessels thereby releasing microRNAs which in turn destroy the cells of the heart muscle.

Pregnancy continues to be a source of fascination for mankind due to the intimate way it is linked to our very existence. A pregnant woman attracts attention wherever she
goes, by evoking an image of both the strength and fragility of the female sex and inevitably arouses the curiosity of those around her. Pregnancy is an experience that many women are impatient to experience while others fear the little aches and pains associated with it. Although the event heralded by pregnancy is described as a happy one, the nine months of abdominal swelling necessary to reach that point are not all sweetness and light. The so-called "happy" symptoms associated with pregnancy are often not so happy at all: nausea, extreme fatigue, back pain, constipation, heartburn, blood circulation problems and lack of sleep etc. The appearance and intensity of these problems varies from woman to woman or even from one pregnancy to another in the same woman.

Heart disease associated with pregnancy

These "happy" signs of pregnancy are regarded as pleasant most probably because they are quite normal and show that the baby is developing normally. However, doctors need to be very thorough but also capable of detecting whether one or other of these symptoms is exacerbated and could possibly lead to complications later on. **Peripartum cardiomyopathy** is difficult to identify and is a complication that can appear in a woman at the end of pregnancy and up to six months after the birth of the child. This type of heart disease is very infrequent but not so infrequent that it can be classed as a "rare disease" (one case in 5,000), affecting one pregnant woman/young mother in 3,500 in our country. However, it is much more common in Africa and reaches record levels in Haiti where it affects one in three hundred women.

"**Peripartum cardiomyopathy is difficult to detect because the symptoms that characterize it are very similar to the symptoms associated with end of pregnancy and the months following childbirth: breathing difficulties, extreme fatigue, palpitations …**," explains Ingrid Struman, a research associate at the F.R.S.-FNRS and project director at the Unit of Molecular Biology and Genetic Research at GIGA (University of Liege). Nonetheless, it is a disease which can have dramatic consequences. "**It involves the dilation of the left ventricle of the heart which results in reduced pumping function of the heart. There may be an improvement in heart function in the months following the birth but this remains poor among 30% of the women affected by the condition and 10% of them die as a result of it**," continues Ingrid Struman. In addition, the state of the heart worsens in these women during the next pregnancy, with an increased mortality rate of 20%.

The hormone which stimulates milk production is suspected of being at issue

To date, there is no way of determining which women are at risk, nor is there any way of determining which factors trigger peripartum cardiomyopathy. In a study carried out in collaboration with German and South-African researchers, Ingrid Struman’s team has identified a biomarker which makes it possible to distinguish this disease from other cardiac diseases that cause heart failure. The results of this study have been published in the Journal of Clinical Investigation (1). "**In 2007, Denise Hilfiker-Kleiner, a German researcher, showed that a prolactin fragment known as 16K-PRL which is produced in the heart, attacks the blood vessels and heart tissues**, says Ingrid Struman. Produced by the pituitary gland, prolactin is a hormone which is involved in the growth of the mammary glands and the stimulation of milk production.

In the context of her research on tumor angiogenesis, Ingrid Struman studied this hormone and, as part of a program of excellence for the Wallonia region, began to take an interest in microRNAs. "**This is why Denise Hilfiker-Kleiner contacted us and how we developed the project on peripartum cardiomyopathy somewhat by accident**, explains the scientist. Although the role played by the 16K-PRL fragment in this disease was well-
established, the mechanisms by which it affects the tissues of the heart had remained a total mystery up to now. This is precisely one of the mechanisms which Ingrid Struman and her colleagues have identified.

**When microRNAs attack the heart tissues**

"We used mice with genetically modified hearts (knockout mice for the STAT3 gene). These mice spontaneously developed post-partum cardiomyopathy. After a first gestation, one third of the mice died", continues Ingrid Struman. "We took blood and heart samples from these knockout mice and we observed particularly high levels of microRNA-146a. Then when we injected the mice with microRNA antagonists (anti-microRNAs), the normal phenotype of the mice was restored". This cumulative analysis of the measurement of the left ventricle in terms of microRNA levels leaves no doubt about the role of the latter in peripartum cardiomyopathy.
But what is the link between the 16K-PRL prolactin fragment and microRNA-146a? "On one hand the prolactin fragment destroys the blood vessels, and on the other it releases microRNAs which in turn destroy the cells of the heart muscle", replies Ingrid Struman. "Therefore there is a transfer of microRNAs from the endothelial..."
cells of the blood vessels to another type of cell, the heart cells. This implies that the microRNAs are to be found outside the cells for a period of time where they can become blocked”, declares the researcher.

Up to now, one of the solutions used to try to reduce the risk of death in women affected by peripartum cardiomyopathy has been to prevent the production of prolactin by treatment with drugs. Unfortunately, this type of treatment also stops milk secretion and prevents women affected by the disease from breast-feeding their babies. "Our South-African collaborator has demonstrated that the majority of mothers in these countries refuse not to breast-feed and opt to take the risk. It is not in their culture to bottle-feed their young and they do not have the means or facilities that we have here to do that", explains Ingrid Struman.

**Breast-feeding without risk for the heart**

From a therapeutic point of view, blocking the 146a-microRNAs would enable mothers to breast-feed their babies without any risk despite the appearance of peripartum cardiomyopathy.

"This is a good example of “translational research”, that is to say basic research which leads on to more applied research", emphasizes Ingrid Struman. “From purely basic research into the mechanisms involved in
angiogenesis, we managed to identify a biomarker that makes it possible to detect a disease and which can eventually serve as a therapeutic target for its eventual cure”.

As the discovery of microRNAs and the important role they play in biological processes is relatively recent, there are as yet no anti-microRNAs on the market. “The first anti-microRNAs are still at the clinical trials phase. However, there has been a marked increase in the use of microRNAs as biomarkers. Their great advantage is that they are very stable. These are small RNAs protected by a vesicle called an exosome”, indicates Ingrid Struman. She explains that the type and structure of the medicinal products used to neutralize the different microRNAs identified up to the present are very similar. Once an anti-microRNA has been perfected and tested, it should be easy to rapidly create and produce other microRNAs-including the one involved in peripartum cardiomyopathy.