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SPOTLIGHT REVIEW

Maternal cardiac metabolism in pregnancy

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Abstract Pregnancy causes dramatic physiological changes in the expectant mother. The placenta, mostly foetal in origin, invades maternal uterine tissue early in pregnancy and unleashes a barrage of hormones and other factors. This foetal 'invasion' profoundly reprogrammes maternal physiology, affecting nearly every organ, including the heart and its metabolism. We briefly review here maternal systemic metabolic changes during pregnancy and cardiac metabolism in general. We then discuss changes in cardiac haemodynamic during pregnancy and review what is known about maternal cardiac metabolism during pregnancy. Lastly, we discuss cardiac diseases during pregnancy, including peripartum cardiomyopathy, and the potential contribution of aberrant cardiac metabolism to disease aetiology.

Keywords Pregnancy • Heart • Metabolism • Peripartum cardiomyopathy

This article is part of the Review Focus on Pregnancy-mediated Heart and Vascular Disease.

1. Introduction

Cardiac complications of pregnancy are increasingly common and increasingly recognized. For example, as the management of paediatric diseases has improved, more and more women are entering pregnancy with pre-existing cardiac conditions, including valvular disease and cardiomyopathy. Pregnancy also independently poses an intense challenge to the cardiovascular system. Large haemodynamic changes increase cardiac workload throughout pregnancy, and neurohormonal changes contribute to the unique vascular pathologies found in pregnant women, including a propensity to blood clotting, haemorrhage, and pre-eclampsia. At the same time, maternal metabolism is also dramatically altered in order to support the robust energetic needs of the growing foetus, affecting all maternal organs, including the heart. The relationship between maternal cardiac metabolism and cardiac pathologies during pregnancy and the postpartum period is only beginning to be understood. We review here what is known about cardiac metabolism during pregnancy and discuss potential roles of altered metabolism in maternal cardiac pathologies, including peripartum cardiomyopathy (PPCM).

2. Systemic metabolism

Before specifically discussing the heart, a review of systemic metabolic changes during pregnancy is useful. Remarkable metabolic shifts occur during pregnancy, serving largely to support foetal needs and to maximize maternal efficiency.[1–4] The metabolic needs of the foetus peak in the third trimester during the phase of greatest growth. Maternal metabolism during early gestation is thus largely anabolic, in essence hoarding nutrients in preparation for the upcoming demands. Late in gestation, maternal metabolism becomes largely catabolic, shunting nutrients to the rapidly growing foetus (*Figure 1*).

The energetic cost of pregnancy is highly variable, but on average, in developed countries with free access to food, it is in the order of 80 000 kcal.[1,5] Nearly half of the cost is taken up in maternal fat storage, on average a gain of 3.5 kg, which occurs primarily during the anabolic first half of pregnancy.[1,4] Another roughly half of the cost of pregnancy supports the synthesis and growth of the foetus, which is reflected in an increased maternal basal metabolic rate of 60% or more during the catabolic second half of pregnancy, reaching ~250 kcal/day near term.[6,7] Ultimately, the conceptus itself contains <10% of the total energetic cost of pregnancy.

Glucose handling changes dramatically during pregnancy.[1–4] The delivery of substrates to the placenta dictates the rate of foetal growth, and glucose is the preferred substrate of the foetus.[3,8] Maternal insulin resistance develops, usually early in pregnancy, thereby limiting maternal glucose consumption and allowing shunting of most of the glucose to the foetus. Hyperinsulinaemic euglycaemic clamps, the gold standard for evaluating insulin sensitivity, reveal as much as 80% decrease in insulin sensitivity late in pregnancy.[4,9–11] This may in fact be an underestimate because glucose is consumed by the foetus independently of insulin. Pregnancy is thus marked by insulin resistance on par with that found in diabetic patients. Insulin resistance in the maternal liver increases gluconeogenic output by 30%. At the same time, insulin resistance in muscle, the largest sink for glucose in the body, limits glucose consumption by the mother.[12] And insulin resistance in adipose tissue dramatically increases lipolysis, providing fatty acids as an alternative fuel for maternal consumption and glycerol as a gluconeogenic substrate

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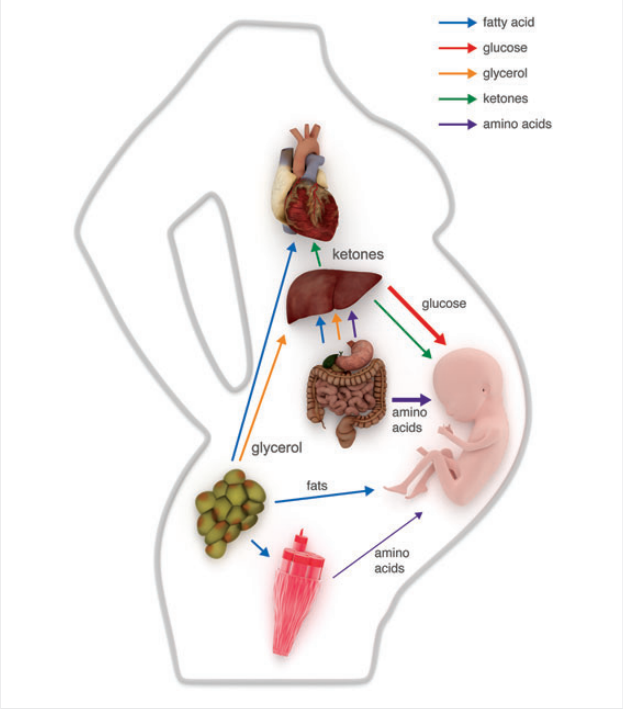

Figure 1 Metabolic changes during late pregnancy. Late pregnancy is marked by maternal catabolism that serves to support the dramatic anabolic growth of the foetus. The liver uses glycerol and (less so) amino acids to make glucose for the foetus and consumes fats, generating in the process ketones that are usable by the brain, muscle, and foetus. Adipose tissue releases fatty acids for consumption by both the liver and muscle. The foetus uses amino acids, fats, and roughly half of incoming glucose for anabolic growth, while largely relying on the other half of glucose for energetic needs.

the liver. Glycerol is the preferred gluconeogenic substrate during pregnancy, thereby preserving amino acids for foetal growth. In short, pregnancy reprogrammes maternal metabolism to maximize shunting of glucose to the foetus. Foetal consumption is extensive enough that maternal fasting glucose decreases by 10% in late pregnancy, despite the insulin resistance.

Insulin levels rise during pregnancy, as early as second trimester, and as much as two-fold or more by term.[8] This may in part reflect the peripheral insulin resistance, analogous to the elevated levels of insulin seen in type II diabetic patients. In addition, β-cell secretogenic function is directly affected by pregnancy as well. Glucose-induced secretion of insulin is thus elevated three-fold in late pregnancy. This reflects in part a 10–20% increase in β-cell mass, a function of both cellular hypertrophy and hyperplasia.[13,14] However, most of the effect reflects greater per-cell insulin synthesis and secretion, though the mechanisms remain incompletely understood.

Nitrogen balance is also significantly altered during pregnancy.[1] Pregnancy generates, between mother and foetus, an average of 1 kg of protein.[15] There is little maternal storage of protein during early gestation, unlike with fats. Negative nitrogen balance, reflected in decreased urea secretion, therefore occurs primarily during late gestation.[16] Amino acids are spared from use as gluconeogenic substrates in the liver, despite the insulin resistance and overall catabolic state. Consumption of branched chain amino acids decreases, while protein synthesis is elevated by 25% in the third trimester.[17]

Serum lipids increase dramatically during pregnancy.[18] Triglycerides are elevated two- to four-fold, total cholesterol by 25–50%, and LDL by 50%.[4] Pregnancy thus generates a relatively atherogenic lipid profile, which may contribute to the propensity for endothelial damage during pregnancy. Experiments with hyperinsulinaemic euglycaemic clamps confirm that net lipogenesis occurs in early gestation, while late gestation is marked by net lipolysis and higher turnover of glycerol, consistent with insulin resistance. Increased lipolysis sends free fatty acids to the liver, where they are either oxidized or packaged as triglycerides in VLDL particles. The high flux of fatty acids in the liver renders pregnant women prone to ketosis, again likely an adaptive response to preserve protein in late pregnancy. Fatty acids become the chief source of maternal fuel during late pregnancy, and to a large extent dictate how much other fuel is available for foetal growth. In addition, placental lipoprotein lipase can elicit fats from circulating lipoprotein particles for foetal use. Levels of circulating triglycerides therefore correlate well with foetal weight, and hyperlipidaemia in the third trimester is the best predictor of large-for-gestational-age foetus.[19]

The growing foetus also appropriates a number of other critical micronutrients, in addition to sugar, fat, and proteins. For example, foetal red blood cell requirements for iron, ~500 mg mostly during late gestation, necessitate more than five-fold increase in daily maternal absorption of iron.[20] Hepcidin, the major hormone regulating iron homeostasis, inhibits gut absorption of iron and hepcidin is nearly undetectable in late pregnancy.[21,22] Similarly, the foetal skeleton undergoes mineralization in the last few weeks of gestation, driving large shifts in calcium mobilization, up to 300 mg/day near term.[1,23] Maternal gut absorption of calcium dramatically increases, likely in large part via vigorous and PTH-independent secretion of 1,25-dihydroxy-vitamin D from the placenta.

The mechanisms underlying these profound metabolic changes remain surprisingly incompletely understood. Complex and integrated placental secretion of hormones likely orchestrates most of the changes. β-human chorionic gonadotropin is first elicited, followed by human placental lactogen (hPL), chorionic somatotropin, oestrogen, progesterone, prolactin, and cortisol, all of which have been implicated in causing insulin resistance. The placenta also elicits numerous cytokines, many of which are known to contribute to insulin resistance during diabetes.[24] For example, of all placental hormones measured during pregnancy, TNFα most closely correlates with insulin resistance, although this observation is complicated by the fact that 90% of measured TNFα originates from the mother.[25] Elevated serum fatty acids may also contribute to insulin resistance, as in type II diabetes. Molecular changes in the skeletal muscle also parallel those found in diabetes: binding by insulin is not altered, but tyrosine phosphorylation of the insulin receptor is decreased and inhibitory serine phosphorylation of IRS1 is increased.[4,26]

In summary, abundant systemic metabolic changes occur during pregnancy, generally to the benefit of voracious foetal metabolic demands. Early pregnancy is largely anabolic, while general catabolism, more pronounced metabolic changes, and rising insulin resistance mark late pregnancy. The molecular mechanisms underlying these changes are likely largely hormonal, but remain poorly understood.

3. Normal cardiac metabolism

Uninterrupted cardiac contraction is essential for providing oxygen and nutrients to the body. The heart thus has high metabolic demands, among the highest in the body. Moreover, with minimal ATP reserves

and complete ATP turnover approximately every 10 s, the heart heavily depends on a continuous energy supply.[27] Thus, tight metabolic regulation is critical to ensure that the needs of the myocardium are met. The reader is referred to a number of excellent reviews for comprehensive discussions of this complex topic.[27–29] A brief overview is provided below.

Fortunately, as a 'metabolic omnivore', the heart can utilize many different types of energy substrates, including carbohydrates, lipids, ketone bodies, and amino acids (*Figure 2*). The decision to use certain substrates depends on both environmental conditions and substrate availability. For example, during strenuous exercise in which lactate concentrations are high in the blood, the heart predominantly utilizes lactate.[30] In contrast, prolonged fasting raises ketone concentrations, and the heart, like the brain, becomes heavily dependent on ketone consumption.[31] Under normal physiological conditions, in which oxygen and fuel supply is plentiful, the main myocardial fuel is fatty acids. This satisfies ~70% of the energy needs, with the remaining 30% supplemented by glucose.[27] Interestingly, glucose uptake can be largely channelled through the glycogen pool prior to conversion to pyruvate,[32] and fatty acid uptake is largely channelled through the triglyceride pool prior to β-oxidation.[28,33,34] These intracellular fuel pools, though limited, are significantly tapped during acute increases in workload, such as in exercise.

The vast majority of substrate catabolism converges on the generation of the common mitochondrial intermediate, acetyl CoA, via for example β-oxidation (for fats) or glycolysis (for glucose).[27] Acetyl CoA then enters the Krebs cycle, yielding CO_2 and reducing equivalents in the form of NADH and FADH. These reducing equivalents deliver electrons to the electron transport chain, which then couples the highly favourable reduction of free oxygen into water with the generation of a proton gradient across the inner mitochondrial membrane. Dissipation of this gradient is then used to drive the formation of ATP from ADP. The complete oxidation of a molecule of glucose thus can yield >30 ATPs, compared with a net yield of only two ATPs if limited to glycolysis.[27] Fats, the chief cardiac fuel, can only be consumed via mitochondrial oxidation.[28] Mitochondria are thus vital to sustain the metabolic demand of the heart. Approximately one-third of cardiac volume is made up of mitochondria. More than 95% of the ATP generated in the heart is derived from oxidative phosphorylation in the mitochondria.[28] In addition to fuel catabolism, mitochondria also play critical roles in cell survival, death, and calcium homeostasis. Thus, precise regulation of the complex metabolic pathways within the heart is pivotal to ensure working and efficient mitochondria.

Mechanisms that dictate the choice of substrate by the heart remain incompletely understood. A leading factor in substrate choice is simply circulating substrate availability, reflecting the omnivorous nature of the heart. So, for example, high use of fatty acids during exercise reflects the high rate of lipolysis in adipose tissue and consequent elevated circulating triglycerides and free fatty acids. But a number of additional regulatory mechanisms exist. The PI3K/Akt pathway, for example, is critical for control of glucose uptake in most tissues, including the heart. Usually in response to insulin signalling, activated Akt triggers the translocation of glucose transporter type 4 (GLUT4)-containing vesicles to the plasma membrane, thereby stimulating glucose uptake.[35] Three Akt isoforms exist, of which Akt1 and 2 are expressed in the heart. Interestingly, these isoforms appear to handle separately cardiac growth and metabolism: Akt1 mediates growth in response to physiological and pathological signals, while Akt2 largely controls glucose handling, likely in large part via GSK3β.[36] The AMP-activated protein kinase (AMPK) pathway has also been studied extensively.[37] AMPK acts as a cellular fuel gauge, sensing AMP/ATP ratios and ADP/ATP ratios, and reacting to a low energy state by activating ATP-generating processes.[38] Exercise is the best-known physiological activator of AMPK.[39] Activation in the heart of AMPK, like Akt, leads to translocation of GLUT4 and increased glucose uptake, as well as glycolysis.[40] AMPK activation also increases both fatty acid import and oxidation, by promoting translocation of the fatty acid transporter CD36 to the plasma membrane, and by antagonizing ACC, an inhibitor of fat transport into the mitochondria.[40]

In addition to allosteric enzyme regulation, control of metabolic flux in the heart is also regulated at the transcriptional level. The peroxisome

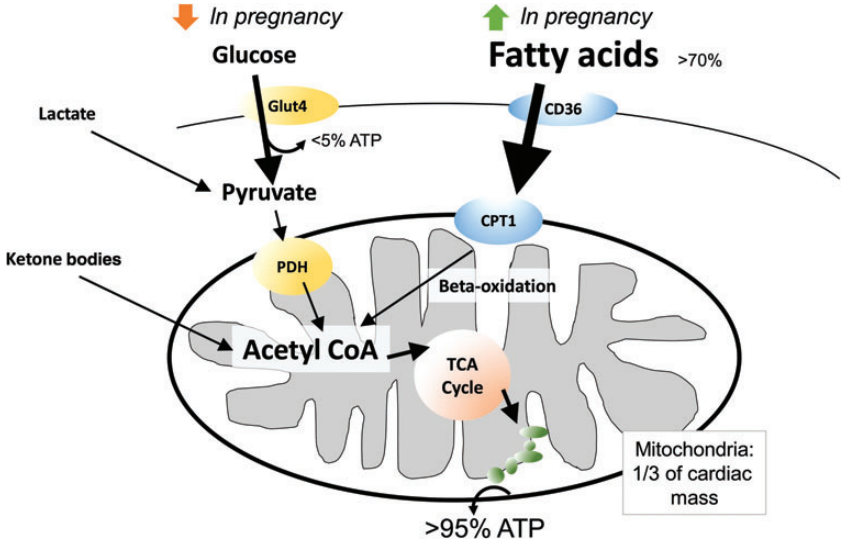

Figure 2 Cardiac metabolism. Cardiomyocytes are 95% oxidative, consuming fuels in mitochondria to generate ATP. Under normal conditions, >70% fuel consumed are fatty acids, but cardiomyocytes are omnivorous and can consume any number of other fuels. Under pregnancy conditions, cardiomyocytes increase utilization of fatty acids while decreasing glucose utilization. PDH, pyruvate dehydrogenase; CPT1, carnitine palmitoyltransferase; TCA, tricarboxylic acid cycle.

proliferator-activated receptors (PPAR), members of the nuclear receptor family of transcription factors, have been most studied.[41] Various fatty acids, for example, bind to PPARα and stimulate its transcriptional activation of genes involved in fatty acid import (e.g. CD36), transport into the mitochondria (e.g. CPT1b), and β-oxidation (e.g. MCAD). Another key transcriptional regulator of metabolism in the heart, as in many other tissues, is the PGC-1 (PPAR-γ coactivator 1) family of transcriptional co-activators, of which PGC-1α is the best studied.[42–44] Constitutive overexpression of PGC-1α in the heart leads to increased mitochondrial biogenesis, respiration, β-oxidation and expression of genes involved in oxidative phosphorylation.[42,45] PGC-1α binds to and co-activates PPARs, oestrogen-related receptors (ERRs), and numerous other transcription factors, thereby co-ordinating multiple pathways including fatty acid consumption (largely via coactivating PPARs), mitochondrial biogenesis (via NRF1/2 and ERRα), and vascular density (via ERRα).[33,46] Cardiac-specific deletion of PGC-1α shows that despite normal mitochondrial content, there is a decrease in oxidative phosphorylation and contractile function, and an increased susceptibility to heart failure, suggesting the vital role of PGC-1α in cardiac function and metabolism.[43,47,48] Cardiac-specific deletion of PGC-1α also leads to PPCM,[48] as discussed in more detail in following sections. In summary, the heart is profoundly dependent upon mitochondria and oxidative metabolism. Although it normally primarily consumes fatty acids, it can consume nearly any fuel type to satisfy its avid metabolic needs.

4. Haemodynamic changes during human pregnancy

Cardiac metabolism is altered during pregnancy in order to accommodate both foetal needs and increased demands for cardiac work. The latter reflects the large haemodynamic shifts that occur during pregnancy. Some uncertainty remains over the magnitude and direction of these shifts despite numerous studies because inconsistent experimental conditions have often led to contradictory measurements.[49] The discrepancies are likely attributable to a number of factors, including (i) small sample sizes often lead to conclusions more relevant to individual profiles rather than to the general population. (ii) Maternal age, height, BMI, and parity, which can result in varying degrees of cardiac changes, are not always controlled for.[50–53] (iii) Different population groups have different basal cardiac values. For example, young healthy African Americans have lower resting cardiac indices and higher resting systemic vascular resistance than their Caucasian counterparts.[54,55] (iv) The maternal position greatly affects echocardiography, because the supine position can obstruct the inferior vena cava and decrease cardiac preload.[56,57] (v) Other methods, such as Holter monitor, thoracic electrical bioimpedance, catherization, and the thermodilution technique, have also been widely used, with varying results.[58–62] (vi) Lastly, many haemodynamic studies use, for practical reasons, the early pregnant or postpartum stage as comparison controls, but important alterations in cardiac parameters can still be detected at these stages.

Despite these significant variabilities, some haemodynamic changes emerge as consistent and reproducible (*Figure 3*). Both blood volume and red blood cell mass increase, leading to increased preload.[63] Cardiac output increases by 20–50%, starting as early as 5 weeks of gestation and peaking by mid- to late pregnancy.[64–70] Reversal can be seen as early as 2 weeks postpartum.[65] Increased cardiac output results from both an increase in heart rate by ∼15–30% by 5 weeks of gestation and an increase in stroke volume by 15–25% by 8 weeks of gestation.[64,65,67,69,71] Total vascular resistance decreases throughout pregnancy, with a >30% decrease reported as early as 8 weeks gestation compared with pre-pregnancy.[45,64,69,70] The drop in vascular resistance is largely due to increased blood flow in the uteroplacental circulation. In addition, the hormonal milieu of pregnancy leads to the secretion of various vasodilators, such as nitric oxide (NO) and prostaglandins, which cause a drop in the peripheral resistance.[63,72–74] Systolic blood pressure, for the most part, remains unchanged, whereas diastolic blood pressure is decreased initially, reaching its nadir around the second trimester, before increasing back to baseline during the last trimester.[52,62,66,67,71,75,76] Consequently, the mean arterial pressure (MAP) is reduced initially as well, but increases by the end of pregnancy.

Cardiac function, both systolic and diastolic, must be affected by the increase in preload and decrease in afterload of pregnancy, but different studies surprisingly come to quite different conclusions. The limited data on diastolic function during pregnancy have been inconsistent; some studies have reported a decrease in diastolic function near the end of pregnancy, while others have reported minor to no changes.[50,52,77–80]

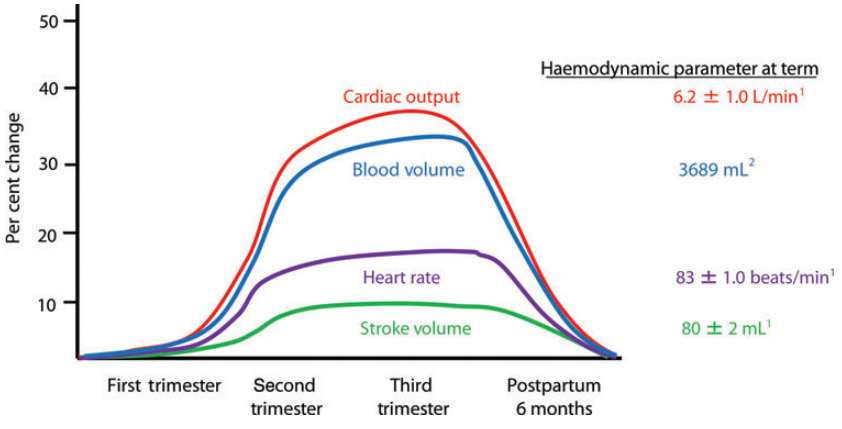

Figure 3 Haemodynamics changes during pregnancy. Cardiac output, heart rate, stroke volume, and blood volume all increase between 5 and 8 weeks of gestation, peak by mid-pregnancy, and is sustained until the end of pregnancy. These parameters are reversed by 6 months postpartum. 1, Clark *et al.*[59]; 2, Hytten and Paintin.[114]

While systolic function is better scrutinized, it is similarly inconsistent: increases, decreases, and no change have been reported.[50,52,67,71,80] For example, ejection fraction has been reported with much variability, with increases, decreases, and no change described with comparable frequency.[52,53,71,78] This aspect of cardiac changes during pregnancy thus remains incompletely defined.

On the other hand, it is clear that important morphological adaptations occur in the heart during pregnancy. By the end of pregnancy, there is enlargement in all four chambers and all valves.[63] Atrial enlargement begins in early pregnancy and peaks around 30 weeks of gestation.[78] This likely reflects the increase in preload and volume overload of pregnancy. Left ventricular end-diastolic dimension (LVEDD) increases by week 24 of gestation by ~10%.[70] Left ventricular mass increases by as much as 50%, peaking around the third trimester.[52,53,70] The end-diastolic posterior wall thickness and septal thickness all increase, similar to LVEDD. These adaptations lead to eccentric hypertrophy during pregnancy. The morphological changes reverse by ~6 months postpartum, although not all studies have detected complete reversal by that time.[70,80] The molecular mechanisms underlying cardiac remodelling during pregnancy have not been well studied, and are reviewed in the accompanying review by Dr Leinwand. In summary, the heart of a pregnant woman faces significantly altered haemodynamic forces, likely demanding equally significant alterations in metabolism (*Table 1*). The magnitude of these numerous haemodynamic and morphological changes differs significantly between studies, underscoring the need for further and more complete studies on this topic.

5. Cardiac metabolism during pregnancy

Remarkably little is known of the metabolic changes that occur in the heart during pregnancy. Studies in humans are almost non-existent. As noted above, cardiac mass increases by as much as 50% during pregnancy, a process that requires energy. In addition, combinations of increased preload, increased contractility, and decreased afterload lead to increases in cardiac output of ~20–50%. Cardiac work *per se* (operationally defined as cardiac output × afterload, or MAP) increases as well, but only 20–30%, because MAP drops during pregnancy. Strikingly, despite these increases in energetic demands, cardiac mean oxygen consumption (MVO_2) only increases by ~15%, at least in dog models.[81] The efficiency of cardiac work thus increases by ~25% during pregnancy. How increased efficiency is achieved is not known. The increase in oxygen consumption is mostly accommodated by increased coronary blood flow, rather than increased extraction, and coronary arterioles become more sensitive to stress-induced vasodilation in pregnancy.[82]

The choice of fuel use by the heart also changes dramatically during pregnancy. Studies in rats in the 1990s showed that glucose utilization declines 75% by late pregnancy.[83,84] Interestingly, the decline began early in pregnancy and progressed throughout pregnancy, peaking in late pregnancy. Metabolic changes thus do not temporally parallel haemodynamic demands, but rather parallel foetal metabolic demands. In studies with pregnant dogs, glucose oxidation in late pregnancy was less markedly reduced than that in rats, but fatty acid oxidation nearly doubled (from 5 to 10 mcM/min).[81] The generation of ATP in late pregnancy thus comes almost exclusively from burning fats (*Figure 2*). Thus the heart, like skeletal muscle, exhibits relative insulin resistance during pregnancy.

The mechanisms underlying the above metabolic changes are not known. Morphological studies are scant and have not provided significant insights, other than the noted cardiac hypertrophy. Mitochondria appear morphologically normal during pregnancy, both in intact animals and in isolated cardiomyocytes.[85] The suppression of glucose oxidation does not reflect inhibition of pyruvate dehydrogenase (PDH), as PDH activity remains normal.[84] Circulating glucose levels are lower, but only slightly so, and thus unlikely to explain the markedly lower glucose influx. Total levels of GLUT4 during pregnancy are decreased,[86] but levels at the plasma membrane have not been reported. Another possible explanation may simply be the high influx of free fatty acids, which would be predicted to inhibit glucose consumption, as originally described by Randle *et al.*[87] More likely, however, specific reprogramming occurs, as suggested by the observation that isolated cardiomyocytes from pregnant rats increase their contractility in response to pyruvate and lactate more than do cells from non-pregnant controls.[85]

A few molecular studies have been undertaken. Cardiac endothelial nitric oxide synthase (eNOS) activity appears to increase during pregnancy, perhaps explaining the higher tendency of arterioles to dilate to sheer stress.[82] NO has been shown to potentially affect cardiac metabolism

Table 1 Maternal serum concentrations of energy substrates in non-pregnant controls, early, and late pregnancy

	Not pregnant	Early pregnancy (5–12 weeks)	Late pregnancy (>32 weeks)
BMR (kJ/24 h)[7]	5430 ± 660[a]	5540 ± 660	7180 ± 1180
Plasma volume (mL)[114]	2699[b]	2768	3689
Serum values			
Fasting glucose (mmol/L)[115]	4.6[c]	4.2	3.9
Fasting insulin (μU/mL)[115]	5.5[c]	4.5	7.5
Free fatty acids (μEq/L)[116]	n.r.	814	900
Triglycerides (mg/dL)[117,118]	77 ± 34	79 ± 27	245 ± 73
LDL (mg/dL)[117,118]	99 ± 23	90 ± 17	136 ± 33
HDL (mg/dL)[117,118]	69 ± 10	67 ± 12	81 ± 17

n.r., not reported; BMR, basal metabolic rate.
[a]Pre-pregnancy.
[b]6–8 weeks postpartum.
[c]10–12 weeks post-natal.

directly and to promote mitochondrial function in contexts outside the heart.[88–90] Administration of L-NAME, an inhibitor of eNOS, to late pregnant dog hearts decreased fatty acid uptake and oxidation back to non-pregnant levels, while increasing glucose uptake.[81] Higher cardiac NO levels during pregnancy may thus explain the observed metabolic shift away from glucose, but the underlying mechanisms are not known. Akt and downstream mTOR are also activated in murine pregnancy, but which isoforms are responsible has not been teased apart.[91] It may be, for example, that decreased Akt2 contributes to blunted glucose uptake, while increased Akt1 mediates growth. Finally, molecular changes also likely occur on the side of ATP consumption. For example, the late outward potassium current slows in late pregnant rats and mice, likely explaining the prolonged QT interval seen on ECGs.[85,92]

Pregnancy also drastically alters the maternal hormonal milieu, including dramatic increases in oestrogen, progesterone, prolactin, and placental hormones. As noted above, many of these have been implicated in causing systemic insulin resistance during pregnancy, but their effects on cardiac metabolism during pregnancy have not been studied. The effect of oestrogen on fatty acid metabolism has been explored in the context of hormone replacement therapy, where it appears to increase cardiac fatty acid utilization while not affecting glucose metabolism.[93] Oestrogen may thus have a similar effect during pregnancy.

Clearly, molecular understanding of metabolic changes in the maternal heart during pregnancy is in its infancy. Key questions remain unanswered. What upstream mechanisms drive metabolic changes? How do the observed metabolic changes interrelate with morphological changes? How do metabolic alterations during pregnancy reset after delivery? Few data exist on cardiac metabolic changes in the postpartum stage. Are the cardiac metabolic changes of pregnancy beneficial or harmful to the heart? That is, is maternal cardiac metabolism rendered vulnerable in deference to the imperatives of foetal development?

6. Metabolism and pregnancy-associated cardiac disease

Does aberrant cardiac metabolism contribute to cardiac diseases of pregnancy? Myocardial infarction during late pregnancy and the peripartum period is increasingly common, due in part to rising maternal age and other lifestyle changes.[94–98] Surprisingly, women who have a myocardial infarction in this period carry a markedly worse prognosis than age-matched non-pregnant women.[96,98] This clinical observation has recently successfully been modelled in rodents, demonstrating that ischaemia/reperfusion injury in late pregnant rodents leads to a myocardial infarct size approximately four-fold greater than in non-pregnant controls.[99] The mechanisms responsible for this high vulnerability remain unclear, but are likely at least in part metabolic in nature. One strong possibility is that this susceptibility stems from the dramatically higher reliance on fatty acid oxidation, which, in other pathological contexts, has been shown to be detrimental.[100] Late pregnancy and the postpartum period are also marked by significantly higher coagulation activity, which may contribute both to the higher incidence of myocardial infarction in this period and to the typically larger infarct size.

PPCM is another rare but potentially fatal cardiac complication of pregnancy. The disease is characterized by systolic heart failure presenting in the last month of pregnancy or the first 5 months postpartum. It affects anywhere from 1:300 to 1:3000 births, with certain geographic 'hot spots' like Haiti.[95,97] Heart failure can spontaneously resolve, but in about half of the cases it does not, and often leads to cardiac transplantation or death. Recent work has strongly supported the notion that PPCM is caused by vasculo-metabolic dysfunction, triggered by the unique hormonal environment of late pregnancy. At least two complementary mechanisms are proposed to contribute. The first mechanism was uncovered using mice genetically engineered to lack the transcription factor STAT3 in cardiomyocytes. In these mice, the late-gestational hormone prolactin is aberrantly cleaved in the heart to a 16 kDa fragment that is toxic to the cardiac vasculature. Vascular dropout and cardiomyopathy ensue.[101] Strikingly, treatment with bromocriptine, an FDA-approved inhibitor of prolactin, rescues this murine model of PPCM.[48,101] Clinical trials of bromocriptine for PPCM are underway, and an early pilot study showed promising results.[102] The second proposed mechanism (not mutually exclusive with the first) was uncovered using mice genetically engineered to lack PGC-1α in cardiomyocytes. In these mice, reduced cardiac expression of the angiogenic factor VEGF renders the heart susceptible to secretion from the late gestational placenta of soluble Flt1 (sFlt1), an endogenous decoy receptor and VEGF inhibitor. The outcome is, again, vascular dropout and PPCM.[48]

These models are complementary and explain a number of clinical observations. PPCM is a disease of late pregnancy and early postpartum, which does not coincide with the onset of haemodynamic stresses of pregnancy (see above). Instead, these models propose that PPCM is triggered by hormones specific to the late gestational period: prolactin (from the pituitary) and sFlt1 (from the placenta). There are likely others as well. PPCM has also long been noted to be strongly associated with pre-eclampsia, a common maternal complication of mid/late gestation that affects 3–5% of pregnancies worldwide.[103] Pre-eclampsia is associated with marked elevations of circulating sFlt1,[104,105] thus potentially explaining the marked increased incidence of PPCM in pre-eclamptic women. Clinically, pre-eclampsia causes cardiac dysfunction directly, independently of blood pressure, and frequently presents with congestive heart failure.[103,105] The two models also both strongly point to the notion that PPCM is a vascular disease, leading to loss or damage of vasculature by as much as 50% in rodent models.[48]

Could metabolic changes be causative for PPCM? As outlined above, strong evidence from two mouse models points to PPCM being at least in part a disease of metabolic insufficiency caused by loss of sufficient delivery of fuel and oxygen to the heart. Other mechanisms likely also exist, such as direct toxicity to the heart by the affected vasculature. For example, 16 kDa prolactin causes vessels to secrete the micro-RNA miR146a, which in turn triggers apoptosis in adjoining cardiomyocytes.[106] Circulating levels of miR146a are markedly elevated in women with PPCM.[106] miR146a also decreases metabolic activity in cardiomyocytes, and reduces expression of ErbB4, thereby interfering with the ErbB receptor system,[106] which is not only known to be cardioprotective, but is also important for glucose transport into muscle cells.[107] Another notion that points to a metabolic impairment beyond the insufficient vascular supply derives from the cardiomyocyte-specific PGC-1α knockout mice that develop PPCM.[48] In addition to regulating VEGF and angiogenesis,[108] PGC-1α potently co-activates PPAR transcription factors to activate components of fatty acid oxidation. Since the gestational heart is increasingly dependent on fatty acid oxidation as primary source of fuel, aberrant fatty acid oxidation in these mice is likely to contribute to PPCM. To what extent this occurs in human cardiomyopathy remains an open question.

Another critical and still open question is what renders one in a thousand women susceptible to these hormonal insults, while the rest tolerate pregnancy well. How the heart reacts metabolically to these insults remains unstudied and an inability to appropriately remodel metabolically may define the predisposition to PPCM. There may also

be a genetic predisposition. PPCM does not follow clear Mendelian inheritance, but some familial associations have been noted.[109,110] Early efforts to identify genetic alterations in women with PPCM are underway and discussed in more detail by van Tintelen *et al.*[111] in this issue. Finally, the host predisposition may also be acquired, thus, for example, by a coincident myocarditis that removes cardiac defences against the hormonal insults described above. Viral infection has long been thought to contribute to PPCM.[112]

Finally, it is interesting, in the context of disease, to ask why stimuli that are typically thought to be pathological do *not* lead to pathology during pregnancy? Physiological cardiac changes of pregnancy and exercise are often 'lumped' together, and contrasted with changes seen in various pathological settings. There is little evidence, however, that exercise and pregnancy have similar effects on cardiac remodelling or metabolism. In fact, the haemodynamic challenges of exercise (relatively short duration, marked tachycardia, high afterload) differ significantly from those of pregnancy (prolonged, moderate tachycardia, high preload, low afterload). The neurohormonal context also differs quite significantly: pregnancy is a sustained high volume/high output state during which, as with states of pathological volume overload, the renin/angiotensin system is hyperactivated.[113] Surprisingly, however, pregnancy does not incite cardiac fibrosis, usually the consequence of chronic angiotensin activation.[113] Presumably, pregnancy-specific defence mechanisms are at play, but their identity is unknown.

7. Conclusions

Pregnancy represents one of the most profound (and most common) processes of system-wide metabolic reprogramming. Despite this, our understanding of metabolic changes in the maternal heart during pregnancy remains limited. Understanding these events could have significant clinical impact because numerous pregnancy-associated cardiac diseases, including myocardial infarction, pre-eclamptic heart failure, and PPCM, likely stem in part from metabolic vulnerabilities. Metabolic alterations have received much attention in numerous cardiac diseases, but none of the above pregnancy-specific diseases have been scrutinized with this lens. The time seems appropriate to fill this gap.

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