MicroRNAs in Pregnancy and Gestational Diabetes Mellitus: Emerging Role in Maternal Metabolic Regulation

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Abstract
Purpose of the Review This review focuses on the recent emergence of microRNAs (miRNAs) as metabolic and developmental regulators in pregnancy and their role in the development of gestational diabetes mellitus (GDM). MiRNAs are short and stable RNA sequences that repress protein synthesis through interference with messenger RNA translation. Recent Findings The placenta produces numerous miRNAs with some of them being released in the maternal circulation. These miRNA genes are encoded into specific clusters and expressed preferentially by placental cells, in a time-dependent manner. They were shown to be dysregulated in plasma and placenta from women suffering from GDM and associated with pregnancy and birth-related outcomes. Summary The discovery of pregnancy-related miRNAs and their respective characterization will provide us with important information as to their function in maternal and placental metabolic regulation. More studies are needed to determine whether they will be useful for early screening of GDM.

Keywords Placenta · Pregnancy · Transcriptomics · Insulin resistance · Epigenetics · Placental injury · Pregnancy complications · Glucose

Abbreviations
AGO Argonaute
Akt AKT serine/threonine kinase
AMPKα1 AMP-activated protein kinase α1 subunit
C14MC Chromosome 14 microRNA cluster
C19MC Chromosome 19 microRNA cluster
DGCR8 DGCR8 microprocessor complex subunit
DIO3 Type 3 deiodinase
DLK1 Delta-like homolog 1
EGFR Epidermal growth factor receptor
ER-α Estrogen receptor alpha
EZH2-β Enhancer of zester homolog 2 isoform beta
GDM Gestational diabetes mellitus
GLUT4 Glucose transporter type 4
HDL High-density lipoprotein
hPGH Human placental growth hormone
hPL Human placental lactogen
HUVEC Human umbilical vein endothelial cells
IG-DMR Intergenic germline-derived differentially methylated region
IGF1 Insulin-like growth factor 1
IRS-1 Insulin receptor substrate 1
IRS-2 Insulin receptor substrate 2
LDL Low-density lipoprotein
lncRNA Long non-coding RNA
MAP K-1 Mitogen-activated protein kinase 1
miRNA microRNA
mRNA messenger RNA
mTOR Mechanistic target of rapamycin
NGS Next-generation sequencing

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Physiological processes behind GDM development. In this added benefit of furthering our understanding of the pathophysiology of GDM. Although they show potential as early biomarker of GDM, their utility as such is still under investigation and remains unproven.

Overview of Gestational Diabetes

Pregnancy is characterized by a progressive insulin insensitivity compensated with a proportional augmentation in insulin production and/or secretion (estimated to be 200–250% of their normal insulin production) [6]. GDM occurs in women unable to compensate insulin sensitivity with sufficient insulin production and/or secretion and who never had diabetes prior to pregnancy, although some studies do suggest the presence of vulnerabilities prior to the disease such as genetic variations in genes related to glucose homeostasis [7]. Furthermore, pregnancies affected by GDM are reported to show an increased risk of short- and long-term complications for both the mother and her child. On the one hand, neonates exposed to GDM show an increased risk of postpartum complications composed of macrosomia, shoulder dystocia, hyperinsulinemia/hypoglycemia, and hyperbilirubinemia. As to long-term effects, they consist of increased risks of developing metabolic diseases such as type 2 diabetes and atherosclerosis and were also linked to obesity [8]. Although current treatments (dietary changes or insulin therapy) are effective in preventing the short-term consequences of GDM (i.e., adverse fetal growth and perinatal outcomes [9]), it remains unclear whether long-term consequences can be prevented [10]. This does lean in favor of a pathophysiological phenomenon taking root before the occurrence of hyperglycemia and thus already in place when diagnosis and treatments are provided.

Some risk factors for GDM have been identified: excess weight and waist girth, older age, non-white ethnic background, and family history of diabetes. These risk factors are unspecific, and even taken together, they remain poor predictors of which women will effectively develop GDM [11]. The strongest single predictor of GDM is a personal history of gestational diabetes mellitus (GDM) is a pregnancy condition diagnosed in previously normoglycemic mothers. The prevalence can reach up to 25% of pregnancies in the USA [1] and up to 15% in Canada [2] (an estimated one in seven births worldwide [3]), with data showing a constant increase for the past 20 years [4]. GDM is associated with short- and long-term health consequences (briefly reviewed below) for both the mothers and their offspring. Among them, childhood overweight and obesity is clearly a worldwide public health problem that deserves our attention. Indeed, the World Health Organization (WHO) Commission on Ending Childhood Obesity [5••] recommended in January 2016 that GDM screening and diagnostic should be improved and done earlier in pregnancy to better address the issue of childhood obesity. MicroRNAs (miRNAs) are a novel class of metabolic regulators with potential roles described only since the last decade. The recent discovery of presence and potential roles of these miRNAs has the potential to provide novel biomarkers to improve current screening and diagnostic strategies with the added benefit of furthering our understanding of the pathophysiological processes behind GDM development. In this review, we will describe the basics of miRNA biology and focus on the potential role of placenta-derived miRNAs in fetal development and maternal metabolism. We will also review current knowledge on the involvement of miRNAs in the pathophysiology of GDM.

Introduction

Gestational diabetes mellitus (GDM) is a pregnancy condition diagnosed in previously normoglycemic mothers. The prevalence can reach up to 25% of pregnancies in the USA [1] and up to 15% in Canada [2] (an estimated one in seven births worldwide [3]), with data showing a constant increase for the past 20 years [4]. GDM is associated with short- and long-term health consequences (briefly reviewed below) for both the mothers and their offspring. Among them, childhood overweight and obesity is clearly a worldwide public health problem that deserves our attention. Indeed, the World Health Organization (WHO) Commission on Ending Childhood Obesity [5••] recommended in January 2016 that GDM screening and diagnostic should be improved and done earlier in pregnancy to better address the issue of childhood obesity. MicroRNAs (miRNAs) are a novel class of metabolic regulators with potential roles described only since the last decade. The recent discovery of presence and potential roles of these miRNAs has the potential to provide novel biomarkers to improve current screening and diagnostic strategies with the added benefit of furthering our understanding of the pathophysiological processes behind GDM development. In this review, we will describe the basics of miRNA biology and focus on the potential role of placenta-derived miRNAs in fetal development and maternal metabolism. We will also review current knowledge on the involvement of miRNAs in the pathophysiology of GDM. Although they show potential as early biomarker of GDM, their utility as such is still under investigation and remains unproven.
we already knew there was much more to a DNA sequence (genomes) than a neatly aligned sequence of purines or pyrimidines. In fact, behind these lines of genetic code lay numerous systems of switches and levers responsible not only for cell identity but also for the very evolution of our species. These systems are now known as epigenetics, which are overall defined as heritable and persistent changes in determinants of gene expression that are independent of DNA sequence (non-genomic) [14]. Because they regulate messenger RNA (mRNA) stability and translation, the recently discovered small non-coding RNA sequences called miRNAs are considered by many as a third epigenetic mechanism. Understanding how this new layer of “genetic” information interacts with the environment and contributes to metabolic regulation in pregnancy and GDM is fundamental. MiRNA biology and roles in pregnancy and metabolic regulation are reviewed below.

The Biology of MiRNAs

MiRNAs, initially labeled as small temporal RNAs (stRNAs) when first discovered in Caenorhabditis elegans [15], are short non-coding, single-stranded RNA sequences (19–25 nucleotides (nt)) derived from the genome. MiRNA genes are mostly transcribed by RNA polymerase II from their own promoter (intergenic) or co-transcribed with other miRNAs (polycistronic miRNA clusters) or with their host protein-coding gene (intragenic) [16•]. The primary miRNA (pri-miRNA), a ~1000-nt capped and polyadenylated transcript containing a stem-loop structure, is cropped by the microprocessor complex to generate a 60–70-nt hairpin-structured precursor miRNA (pre-miRNA) [16•]. The pre-miRNA is exported to the cytoplasm by the Exportin5-RanGTP system and cleaved by the Dicer/TRBP complex to produce an miRNA duplex [16•]. Once loaded onto an Argonaute protein (AGO1–4 in humans), one strand (guide) from the miRNA duplex is selected as the mature miRNA to form the mature RNA-induced silencing complex (RISC), while the other strand (passenger) is degraded [16•]. The canonical miRNA biogenesis pathway has been detailed in Fig. 1. Non-canonical miRNA biogenesis pathways have also been characterized and reviewed in [16•].

The biological function of miRNAs is usually, but not exclusively, attributed to the repression of protein synthesis [17]. The molecular targeting system is based on the principle of RNA interference, where an miRNA guides the mature RISC by (mostly partial) base-pairing to the 3′-untranslated region (UTR) of its mRNA target [17], although targeting can also occur in the 5′-UTR as well as in the protein-coding region of mRNAs [18, 19]. This interaction, which is mainly dependent on the complementarity at the miRNA seed region (i.e., nucleotides 2–8 from the 5′-end of the miRNA) [20], consequently inhibits mRNA translation and promotes mRNA sequestration into processing bodies as well as its degradation (mRNA destabilization and decay, accelerated by mRNA deadenylation and decapping) [17]. Importantly, miRNAs could act synergistically to post-transcriptionally regulate (often, but not always, functionally related) genes [21, 22].

Beyond their classic role in mRNA interference within cells, miRNAs also possess other less well-characterized functions (reviewed in [23] and [24]). For example, a miRNA binding to its target mRNA could promote protein synthesis [25, 26] or regulate gene transcription (likely through recruitment of epigenetic machinery to the targeted gene promoter), nuclear transcript stability (e.g., mRNAs, long non-coding RNAs (lncRNAs), or pre-miRNAs) and alternative splicing events (reviewed in [23]) when reimported into the nucleus. Most importantly, miRNAs can also be exported to the extracellular space and play a role in cell-to-cell communication by either acting locally (as paracrine or autocrine) or at distance (endocrine/exocrine) in a way not too different from hormones [27, 28]. Indeed, miRNAs are present in virtually all biological fluids [29], including plasma, where they are associated to various carriers such as lipoproteins, RNA-binding proteins (AGO2 and nucleophosmin 1 (NPM1)) and microvesicles (e.g., exosomes) and show high stability [30], historically supporting their potential role as biomarkers.

Moreover, miRNAs are implicated in embryonic development [31–33], mostly as temporal regulators [34, 35], and also in regulation of essential physiological/metabolic functions [36, 37]. These discoveries portray miRNAs as dynamic regulators, acting as versatile effectors in many essential cellular and metabolic systems. Experimental investigations into their role in pregnancy and pregnancy-related diseases are relatively new, but they have so far provided us with a new perspective of early placental development and possible pathogenesis of GDM.

Placental MiRNAs in Pregnancy

Pregnancy imposes enormous stresses on the mother’s physiology and instigates numerous physiological changes to accommodate for proper embryo growth. These changes affect notably the maternal cardiopulmonary and renal systems which need to adjust for augmentation of plasma volume, the hepatic system which compensates for the impending hemodilution and risk of bleeding [38], and, more importantly, the endocrine system to increase nutrients’ bioavailability to sustain fetal growth and development [39]. Insulin resistance, which normally occurs in the second half of pregnancy, is implicated in this last process [40, 41]. Although the maternal metabolic adaptations to pregnancy are believed to be, in part, driven by placenta-derived factors [40], an improper response of the maternal metabolism to fetal signals in predisposed women can eventually result in diseases such as GDM or
pre-eclampsia [42, 43]. Interestingly, differences in placenta-associated miRNA expression have been noted in GDM and pre-eclampsia.

Indeed, miRNAs have been described as fine regulators of importance in development and metabolism, and their deregulation in disease states has repeatedly been reported [21]. In the last decade, a particular interest has emerged in understanding the relevance of miRNAs in pregnancy, in terms of biological function and biomarker applicability. Placental miRNAs are mainly (but not exclusively) encoded into three identified miRNA clusters (i.e., C19MC, C14MC, and miR-371-3 cluster) [44, 45]. So far, more than 600 miRNAs dynamically expressed in the human placenta were reported [46•, 47•]. Out of these, many were linked to intracellular functions in trophoblasts such as cell proliferation (miR-378a-5p, mir-376c, mir-141, mir-155, mir-675), apoptosis (miR-29b, miR-182), migration and invasion (miR-378a-5p, mir-376c, mir-195, mir-21, mir-210, mir-34a, mir-29b), and angiogenesis (miR-16, miR-29b, miR-17/92 cluster) [47•–49•, 50•]. These processes are critical for an adequate placentation in
early pregnancy and help in building the interface that will provide an optimal flow of blood for exchanges (e.g., nutrients, oxygen) between the mother and her fetus [48, 50*].

**Chromosome 19 MiRNA Cluster**

Chromosome 19 miRNA cluster (C19MC) is a large cluster of miRNA spanning ~100 kb and mapping to chromosome 19q13.41 in humans. C19MC is exclusive to primates and contains 46 miRNA genes (producing 58 mature miRNAs) expressed predominantly by trophoblasts and later by their differentiated cells in the placenta [44, 45], suggesting an important role of these miRNAs in primate development. Interestingly, the C19MC is regulated by genomic imprinting [51], through DNA methylation of its CpG-rich promoter region (17.6 kb upstream of C19MC) on the maternally inherited allele. Consequently, only the paternally inherited allele is expressed. Although their biological function is not completely elucidated, miRNA members of the C19MC are suspected to play a role in cell proliferation, differentiation, and invasion [44], a function also characteristic of oncogenes, as well as in viral resistance [52*].

In an effort to link the maternal plasma miRNA profile to placenta-related conditions, Kotlabova et al. correlated the miRNAs from C19MC with placental weight (miR-515-3p, miR-517a, miR-517c, and miR-518b) [53] and elevated during labor as compared to the non-labor group (miR-515-3p, miR-517a, miR-517c, and miR-518b). Following this discovery, these miRNAs were studied in pathological conditions such as preeclampsia, placenta previa, placenta abruption, and GDM, to uncover potential indicators of placental injury or status detected in maternal blood samples. Hasegawa et al. found a significant increase of miR-517a with low miR-518b during placenta previa [54]. Hromadnikova et al. later established that plasma upregulation of miR-516-5p, miR-517, miR-520a, miR-525, and miR-526 was a characteristic of preeclampsia and could possibly be linked to placental insufficiency, thus serving as indicators for placental distress [55]. Zhu et al. also reported an increase in both miR-517 and mir-518b during severe preeclampsia [56]. Miura et al. then found that a significant elevation of miR-517c in maternal plasma could discriminate placenta abruption from uncomplicated pregnancies [57]. All of these findings were based on a cross-sectional study design, limiting inferences of cause to effect. One study tested the usefulness of these miRNAs to predict pregnancy outcome/complications. Hromadnikova et al. reported that miR-516-5p, miR-517, miR-518, miR-520a, and miR-526 increase in the maternal circulation detected in early pregnancy (12th to 16th weeks of gestation) was related to a higher risk of placenta insufficiency-related complications such as intrauterine growth restriction and pre-eclampsia [58]. Yet, no current published prospective studies have reported a link between miRNAs in C19MC and the risk of developing GDM. With studies showing increasing links between GDM and pregnancy complications such as preeclampsia [42, 59, 60], discoveries in either field will help us understand placentation and how diverging from normal processes could lead to illness.

**Chromosome 14 MiRNA Cluster**

Chromosome 14 miRNA cluster (C14MC) is located at the imprinted DLK1–DIO3 domain on chromosome 14q32 in humans and contains 52 miRNA genes over 40 kb (producing 63 mature miRNAs) [44, 45]. This cluster is conserved among eutherian species and is also highly expressed in trophoblasts [44, 45, 61]. Conversely to C19MC, C14MC is exclusively expressed from the maternally inherited allele (the paternal allele being methylated) and is regulated by DNA methylation of an intergenic germline-derived differentially methylated region (IG-DMR) located ~200 kb upstream the cluster [45, 62]. A recent study carried on mice with a deletion of the maternally inherited C14MC allele reported partially penetrant neonatal lethality related to deficiency in the maintenance of energy homeostasis at birth (at least partially due to an alteration in hepatic gene expression program), suggesting a role of these miRNAs in the regulation of neonatal metabolic adaptation [63*]. However, the biological relevance of the C14MC members in humans remains unclear and requires further investigation.

**miR-371-3 Cluster**

Another placental cluster is the miR-371-3 cluster, a region spanning 1050 bp located ~25 kb downstream of C19MC. This cluster is exclusive to mammals, contains three miRNA genes coding for six mature miRNAs, and is predominantly expressed in the placenta as well as embryonic stem cells [45], where they have roles in cell cycle maintenance [64, 65], regulation of proliferation, and apoptosis [66, 67]. Beside their role in certain cancers as cell invasion and proliferation factors (similar to C19MC) [68], little is known about their function in the placenta.

Overall, although studies initially conducted in animal models warrant caution when transferring knowledge to humans [46*], promising evidence does support these three clusters to be major contributors in human pregnancy. First, all three have highly conserved sequences in the human genome dating back to our mammalian ancestors [45, 69]. Second, they are preferentially expressed in placental cells
MiRNAs and Gestational Diabetes

In 2011, Zhao et al. first reported significant downregulations of miR-132, miR-29a, and miR-222 in serum collected from women between the 16th and 19th weeks who developed GDM ($n=24$) compared to normoglycemic controls ($n=24$) [80]. Importantly, these results were validated in an internal and two independent cohorts for miR-29a and miR-222, which have been repeatedly associated with diabetes and having a role in the regulation of pancreatic β-cell functionality, insulin sensitivity, and glucose homeostasis [81, 82]. Interestingly, a few years later, Shi et al. (same group) also reported that miR-222 levels were upregulated in omental adipose tissue biopsies (collected at the time of c-section between the 38th and 39th weeks of pregnancy) from women with GDM when compared to normoglycemic controls [83]. miR-222 levels were also positively correlated with maternal serum estradiol concentration (which was found increased in the GDM group) and negatively with estrogen receptor (ER)-α and insulin-sensitive membrane transporter glucose transporter 4 (GLUT4) protein concentration in omental adipose tissue [83]. Experimental validation in 3T3-L1 adipocytes using antisense oligonucleotides provided additional supportive evidence for a role of miR-222 in estrogen-induced insulin resistance in GDM [83].

The same group then reported a significant upregulation of miR-518d (part of the C19MC) concentration in GDM compared to normoglycemic controls and a strong inverse correlation between miR-518d concentration and the protein concentration of peroxisome proliferator-activated receptor-α (PPARα) in full-term placenta [84]. PPARα was demonstrated to be a direct target of miR-518d using a luciferase reporter assay [84]. PPARs are transcription factors regulating genes involved in lipid homeostasis and energy metabolism [85] suggesting that miR-518d expression dysregulation in the placenta may play a role in these systems. Thus, both miR-222 and miR-518d may be miRNAs potentially implicated in GDM pathophysiology.

More recently, Floris et al. reported dysregulation of an epigenetic regulatory feedback loop in cultured human umbilical vein endothelial cells (HUVECs) implicating miR-101 and the histone methyltransferase enhancer of zester homolog 2 isoform beta (EZH2-β) in offspring exposed to GDM [86]. Briefly, they found that HUVECs from fetus exposed to GDM (n = 22) showed decreased functionality, increased miR-101 expression, and reduced EZH2-β concentration as well as histone H3K27 trimethylation [86] compared to controls (n = 24). Although in vitro studies support that increased miR-101 expression is related to the reduced EZH2-β binding to the miR-101 gene promoter and corresponding H3K27 trimethylation decreases, the authors showed that most of the HUVEC dysfunctions observed in GDM (cell apoptotic activities as well as angiogenic and migratory capacities) are
possibly independent of EZH2-β [86]. Persistence of this altered miR-101/EZH2-β circuit and its long-term consequences on child’s health (i.e., risk of cardiovascular disease) remains unclear.

Zhu et al. assessed miRNA levels in plasma from women with GDM (n = 10) compared to normoglycemic controls (n = 10) using next-generation sequencing (NGS) analysis of pooled samples collected between the 16 and 19th weeks of pregnancy [87••]. After validation using real-time quantitative PCR (RT-qPCR), level differences between groups were confirmed for five miRNAs (miR-16-5p, miR-17-5p, miR-19a-3p, miR-19b-3p, miR-20a-5p) [87••]. Gene ontology and pathway analysis predicted these miRNA target genes to be related to insulin resistance (IRS-1, IRS-2, SOS-1, MAPK-1), inflammation (TGF-β signaling pathway), and energy balance (mTOR signalization pathway) [87••]. These miRNAs (except miRNA-16) are part of the miR-17/92 cluster, which has ties to angiogenesis [88] and is also associated with placental development in relation to trophoblasts’ cell cycle pathways by targeting RB1 and SMAD4 [89]. This cluster has been demonstrated to be dysregulated both in placental tissue and in maternal serum in the context of macrosomia [89].

A study from Li et al. identified 29 miRNAs to be differentially concentrated in full-term placenta from women with GDM (n = 15) compared to those showing normoglycemia (n = 15) using a miRNA microarray: results were replicated by RT-qPCR for nine of miRNAs (miR-508-3p being upregulated, and miR-27a, miR-9, miR-137, miR-92a, miR-33a, miR-30d, miR-362-5p, and miR-502-5p being downregulated in placenta exposed to GDM) [88]. These miRNAs were predicted to target genes involved in the EGFR/PI3K/Akt signaling pathway [88], which is important for adequate placental development and fetal growth [90]. Interestingly, protein concentrations of EGFR, PIK3CG, and phosphorylated Akt were increased in placenta exposed to GDM, whereas PIKfyve (a direct target of miR-508-3p) was decreased [88], suggesting an upregulation of the EGFR/PI3K/Akt signaling pathway in GDM-exposed placenta. This may contribute to the significantly higher birth weight reported for newborns exposed to GDM compared to healthy controls in this small case-control study [88].

Finally, Triggestad et al. used a microRNA microarray to identify miRNAs differentially expressed in HUVECs from newborns exposed to GDM (n = 7) as compared to those born to normoglycemic mothers (n = 12) [91]. From 32 miRNAs selected for validation by RT-qPCR (based on variation in miRNA concentration between groups and evidence from literature that these miRNAs have a role in the regulation of metabolic pathways), seven (miR-30c-5p, miR-452-5p, miR-126-3p, miR-130b-3p, miR-148a-3p, let-7a-5p, and let-7g-5p) were found upregulated in HUVECs from newborns exposed to GDM [91]. Interestingly, these miRNAs were predicted to target several genes involved in important metabolic pathways such as insulin/IGF1 signaling, adipogenesis, and endothelial function [91]. In vitro experiments performed in this study also provide support for a role of miR-130b-3p and miR-148a-3p in post-transcriptional regulation of AMP-activated protein kinase α1 subunit (AMPKα1), whose protein concentration is decreased in placenta exposed to GDM [91]. The AMPK complex (of which AMPKα1 is the main functional component) is a central enzyme in energy homeostasis, regulating genes involved in fatty acid synthesis, protein synthesis, and glucose metabolism [92]. Downregulation of AMPKα1 may thus contribute to explain the decrease in fatty acid oxidation previously reported in infants exposed to GDM [93] and might likely increase the child’s risk of developing a cardiometabolic disease later in life.

Objectively, the interest in miRNAs and GDM is rather new with only a few studies published so far. Many are of small sample size (n < 20 per group) but are nevertheless of interest because they are supported by replication and/or functional (in vitro) studies. Large studies are now needed to confirm the role of miRNAs in metabolic regulation in pregnancy and to identify the miRNAs implicated as well as their maternal or placental origin.

Screening and Diagnostic Applications

Plasma miRNAs have demonstrated good qualities as biomarkers since they were demonstrated to be very stable in many bodily fluids and easily amplified as well as analyzed [94]. Interpretation of variations in miRNA profiles has nevertheless proven difficult since quantitative studies on miRNA have, so far, been hard to replicate because of various factors including differences in populations and ethnicities, methodology, and small sample sizes [95]. For now, miR-517 and miR-518b could be regarded as potential indicators of placental injury, a feature that is present in GDM-exposed placenta tissue [78, 96], but the role of these miRNA remains to be tested in GDM specifically. New technologies are now readily available, and their application, such as NGS methods, has the ability to discover novel miRNAs and in turn accelerate the search for viable biomarkers of GDM.

Conclusion

GDM is increasing in prevalence around the world and is associated with an increased risk of obesity and diabetes in offspring affecting health of current and future generations. It is now part of an international growing concern according to the WHO and currently needs to be tackled using innovative strategies. MiRNAs during pregnancy and GDM have been of rising interest in the ever-expanding field of epigenetics and could represent a promising avenue for the discovery of biomarkers and to expand our understanding of GDM.

[91]
pathophysiology. However, work still needs to be done before miRNA panels/profiles for the early prediction of GDM prove clinically relevant. Nevertheless, current studies support the importance of miRNAs in the development of the placenta and their contribution to intercellular communication.

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**Authors’ Contribution** CP reviewed the literature and wrote the manuscript. VD reviewed the literature and revised the manuscript. RG reviewed the literature and revised the manuscript. LB supervised all steps of the review process and revised the manuscript. Each author approved the manuscript.

**Compliance with Ethical Standards**

**Conflict of Interest** Cédrik Poirier, Véronique Desgagné, Renée Guérin, and Luigi Bouchard declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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