European Journal of Clinical Pharmacy

Print ISSN: 2385-409X **Online ISSN**: Applied
Website: https://farmclin.es/

Original Research Article

Biochemical and Hormonal Correlates of Gestational Diabetes Mellitus: Insights into Cortisol, Melatonin, and Glycemic Control

Article History:

Name of Author:
Alok Kumar[1], Divya Shubham[2], Raman Kumar Rana[3], Ezaz Zafar[4]*

Affiliation:
[1]Assistant Professor, Department of Biochemistry, Lord Buddha Koshi Medical College and Hospital, Saharsa, Bihar, India,
[2]Assistant Professor, Department of Obstetrics and Gynecology, Lord Buddha Koshi Medical College, Saharsa, Bihar, India,
[3]PhD Research Scholar, Department of Biochemistry, Katihar Medical College, Katihar, Bihar, India,
[4]Professor, Department of Biochemistry, Katihar Medical College, Katihar, Bihar, India,

Corresponding Author:
Dr. Ezaz Zafar

Email: ezazzafar@yahoo.co.in

How to cite this article:
Kumar A, Shubham D, Rana RK, Zafar E. Biochemical and hormonal correlates of gestational diabetes mellitus: insights into cortisol, melatonin, and glycemic control." European Journal of Clinical Pharmacy, vol. 7, no. 1, 2025.

Received: 12-07-2025
Revised: 24-07-2025
Accepted: 01-08-2025
Published: 19-08-2025

Abstract: ***Background:*** Gestational diabetes mellitus (GDM) is characterized by metabolic and hormonal dysregulation. Beyond insulin resistance, alterations in stress (cortisol) and circadian (melatonin) hormones may contribute to impaired glucose control.
Objective: To evaluate biochemical and hormonal profiles in women with GDM compared to normoglycemic controls and to examine correlations between cortisol, melatonin, and fasting blood glucose (FBG). ***Methods:*** A case–control study was conducted among 240 pregnant women (120 GDM, 120 controls) between 22–32 weeks of gestation. Fasting blood samples were analyzed for FBG (glucose oxidase–peroxidase method), serum cortisol, and melatonin (ELISA). Independent t-tests compared mean values, and Pearson's correlation assessed associations. Statistical significance was set at $p<0.05$. ***Results:*** Women with GDM had significantly higher FBG (208.4 ± 14.6 vs 106.2 ± 8.4 mg/dl, $p<0.001$) and cortisol (704.3 ± 44.8 vs 656.5 ± 40.2 nmol/ml, $p<0.001$), and lower melatonin (26.1 ± 2.6 vs 27.9 ± 2.5 pg/ml, $p<0.001$) than controls. Cortisol correlated positively with FBG ($r=+0.48$, $p<0.001$ in GDM), while melatonin correlated inversely with FBG ($r=–0.41$, $p<0.001$). Cortisol and melatonin were inversely correlated in GDM ($r=–0.35$, $p<0.001$). ***Conclusion:*** Elevated cortisol and reduced melatonin are strongly associated with hyperglycemia in GDM, suggesting disruption of the stress–circadian hormonal axis. These findings highlight potential pathways linking lifestyle, endocrine rhythms, and glycemic dysregulation in pregnancy.

Keywords: Gestational diabetes mellitus, cortisol, melatonin, circadian rhythm, fasting blood glucose

INTRODUCTION

Gestational diabetes mellitus (GDM) is a major metabolic disorder of pregnancy, defined as glucose intolerance first recognized during gestation (McIntyre et al., 2019). The global prevalence of GDM has been increasing steadily, ranging from 5–25% depending on the population studied and diagnostic criteria used (American Diabetes Association, 2023). This rising burden is of clinical concern because GDM is associated with adverse maternal outcomes such as pre-eclampsia, cesarean delivery, and long-term risk of type 2 diabetes, as well as neonatal complications including macrosomia, hypoglycemia, and increased risk of metabolic syndrome in later life (Buchanan & Xiang, 2005; Guariguata et al., 2014).

The pathophysiology of GDM is multifactorial. Classically, pregnancy induces a state of physiological insulin resistance due to placental hormones such as human placental lactogen, estrogen, and progesterone, which enhance lipolysis and ensure glucose availability to the fetus (Catalano, 2014). In women with GDM, this physiological insulin resistance becomes exaggerated, unmasking impaired pancreatic β-cell function and reduced insulin sensitivity (Radaelli et al., 2021). While obesity, advanced maternal age, and family history of diabetes are established risk factors, emerging evidence indicates that stress-related endocrine imbalance and circadian rhythm disruption may also play a pivotal role in GDM pathogenesis (Reutrakul & Van Cauter, 2018; Miller et al., 2021).

Cortisol, the primary glucocorticoid hormone released in response to stress, promotes hepatic gluconeogenesis, enhances proteolysis, and antagonizes insulin action at peripheral tissues. Elevated maternal cortisol levels during pregnancy have been linked to increased fasting glucose and insulin resistance (Kivimäki et al., 2019). Hypercortisolemia may therefore exacerbate glycemic dysregulation in GDM, contributing to poor maternal–fetal outcomes.

In contrast, melatonin, a pineal gland–derived hormone secreted predominantly at night, regulates circadian rhythm and exerts protective metabolic effects. It modulates insulin secretion by binding to melatonin receptors on pancreatic β-cells and improves glucose uptake in peripheral tissues (Cipolla-Neto & Amaral, 2018). Reduced melatonin levels, or disrupted circadian patterns due to shift work, irregular sleep, or environmental light exposure, have been associated with increased risk of type 2 diabetes and GDM (Reutrakul & Van Cauter, 2018). Experimental studies further suggest that melatonin deficiency impairs maternal–fetal glucose regulation, potentially worsening GDM-related complications (Kovac et al., 2020).

The interaction between cortisol and melatonin is also of importance. These hormones are inversely related in healthy physiology, maintaining a balance between stress responses and circadian regulation (Miller et al., 2021). In pregnancy, disruption of this hormonal axis may predispose women to metabolic dysfunction, yet few studies have investigated this relationship in the context of GDM.

Given these gaps, our study aimed to systematically evaluate differences in cortisol, melatonin, and fasting blood glucose (FBG) between women with GDM and normoglycemic controls, and to explore their interrelationships. We hypothesized that women with GDM would demonstrate elevated cortisol, reduced melatonin, and altered correlations with glycemic status, reflecting dysregulation of the stress–circadian hormonal axis.

MATERIALS AND METHODS

Study design and setting: A case-control study was conducted at Lord Buddha Koshi Medical College and Hospital, Saharsa, Bihar, India, between July 2023 and July 2025.

Sample size: 240 pregnant women (120 GDM, 120 controls) recruited between 22–32 gestational weeks.

Inclusion criteria: Pregnant women diagnosed with GDM (cases) and normoglycemic pregnant women (controls).

Exclusion criteria: Pre-existing diabetes, thyroid disease, psychiatric illness, chronic glucocorticoid use.

Data collection:
Clinical details (age, BMI, lifestyle factors) were collected. Blood samples (fasting morning venous) were analyzed for:

- FBG: Glucose oxidase-peroxidase method
- Serum cortisol: ELISA, nmol/ml
- Serum melatonin: ELISA, pg/ml

Statistical analysis: Independent t-tests compared group means. Pearson's correlation assessed associations between hormones and FBG. SPSS v25 used; $p<0.05$ considered significant.

Statistical Analysis
Data were analyzed using SPSS version 25. Descriptive statistics were used for demographic data. Paired t-tests were applied to compare within-group differences, and independent t-tests were used to compare between-group differences. A p-value of less than 0.05 was considered statistically significant. Missing data were handled using the intention-to-treat principle, with last observation carried forward (LOCF) method for imputation.

RESULTS

A total of 240 pregnant women were enrolled in the study, comprising 120 women with GDM and 120 normoglycemic controls. Baseline demographic characteristics, including age, body mass index (BMI), and gestational age, were comparable between the two groups (data not shown). The biochemical and hormonal analyses revealed distinct differences between GDM and control groups, with significant alterations observed in fasting blood glucose (FBG), serum cortisol, and melatonin levels. The detailed findings are presented below.

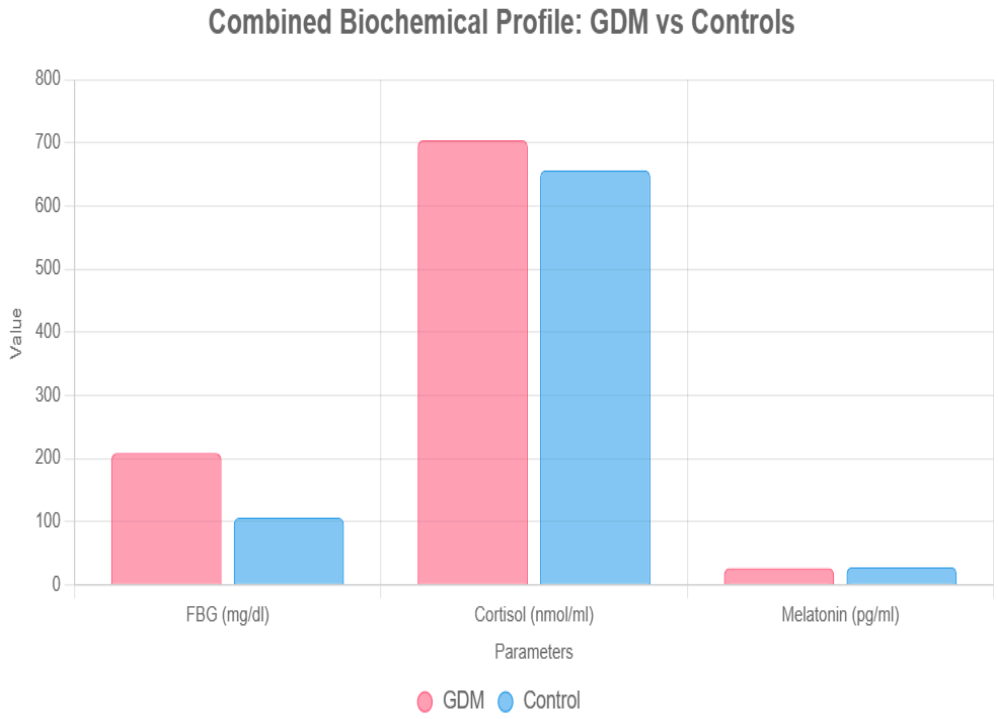
Combined Biochemical Profile

Table 1. Combined Biochemical Profile – GDM vs Controls (n=240)

Parameter	Group	n	Mean ± SD	p-value
FBG (mg/dl)	GDM	120	208.4 ± 14.6	<0.001
	Control	120	106.2 ± 8.4	
Cortisol (nmol/ml)	GDM	120	704.3 ± 44.8	<0.001
	Control	120	656.5 ± 40.2	
Melatonin (pg/ml)	GDM	120	26.1 ± 2.6	<0.001
	Control	120	27.9 ± 2.5	

Women with GDM had significantly higher FBG and cortisol, but lower melatonin compared to controls.

Chart 1: Combined Biochemical Profile



Hormonal Profile by Trimester

Table 2. Hormonal Profile by Trimester – GDM vs Controls

Trimester	Group	n	Cortisol (nmol/ml) ± SD	Melatonin (pg/ml) ± SD	p-value (Cortisol)	p-value (Melatonin)
2nd	GDM	48	695.4 ± 42.8	25.8 ± 2.1	<0.001	<0.001
	Control	50	652.3 ± 40.5	27.4 ± 1.9		
3rd	GDM	72	710.2 ± 45.1	25.1 ± 2.3	<0.001	<0.001
	Control	70	660.8 ± 39.7	27.8 ± 2.0		

In both 2nd and 3rd trimesters, GDM women showed elevated cortisol and reduced melatonin compared to controls.

Chart 2: Cortisol Levels by Trimester

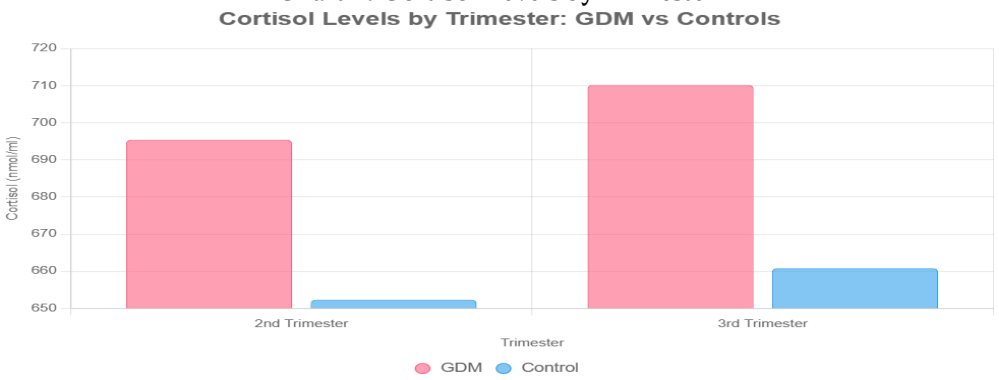
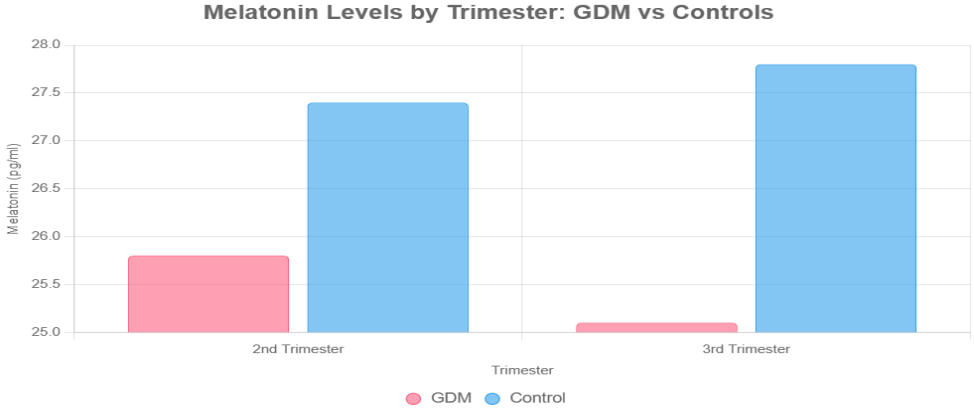


Chart 3: Melatonin Levels by Trimester



Correlations with FBG

Cortisol correlated positively with FBG in both groups, stronger in GDM. Melatonin correlated inversely with FBG.

Table 3. Correlation between Cortisol and FBG – GDM vs Controls

Group	n	r	p-value
GDM	120	+0.48	<0.001
Control	120	+0.32	0.001

Table 4. Correlation between Melatonin and FBG – GDM vs Controls

Group	n	r	p-value
GDM	120	–0.41	<0.001
Control	120	–0.28	0.002

Chart 4: Correlation between Cortisol and FBG

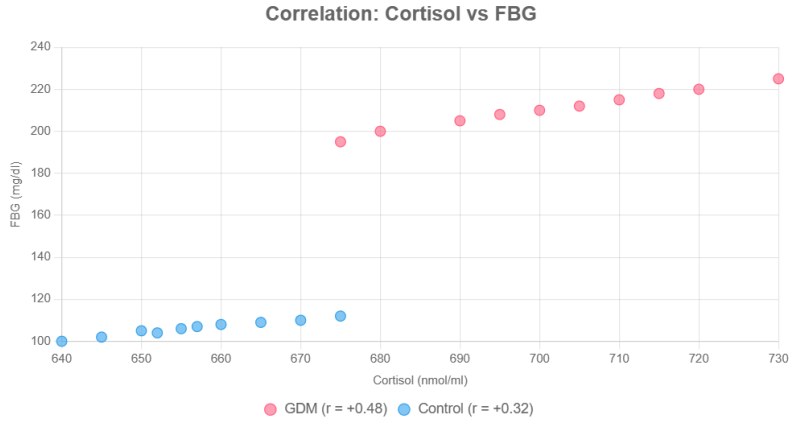
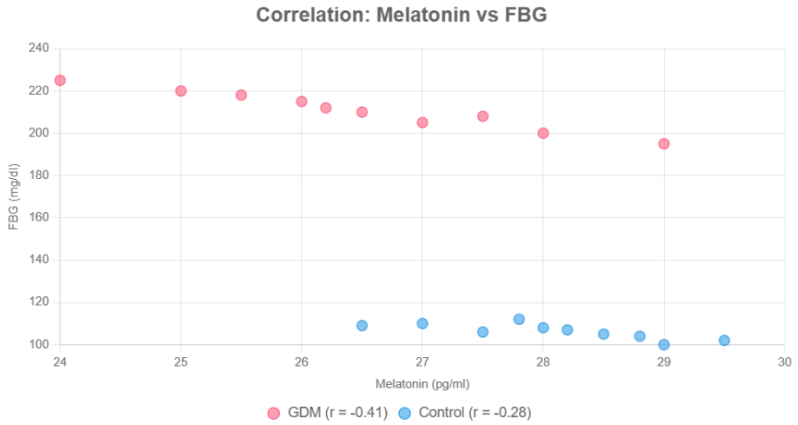


Chart 5: Correlation between Melatonin and FBG



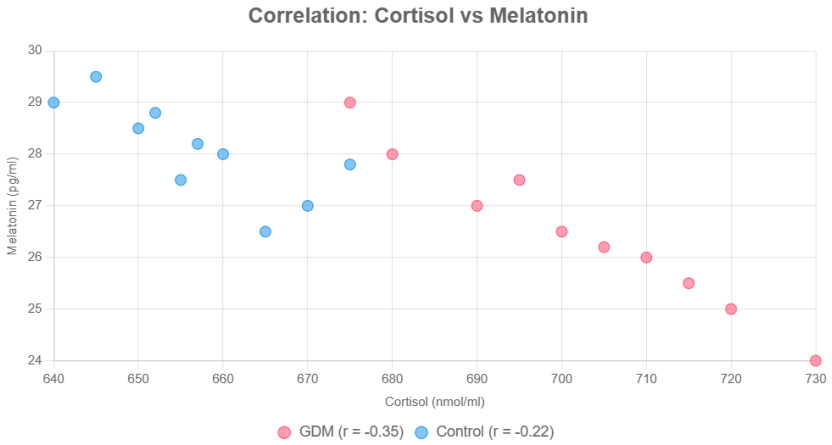
Cortisol–Melatonin Relationship

Table 5. Correlation between Cortisol and Melatonin – GDM vs Controls

Group	n	r	p-value
GDM	120	–0.35	<0.001
Control	120	–0.22	0.015

A significant inverse relationship between cortisol and melatonin was observed, more pronounced in GDM.

Chart 6: Correlation between Cortisol and Melatonin



DISCUSSION

This study highlights significant hormonal dysregulation in women with gestational diabetes mellitus (GDM), characterized by elevated cortisol levels, reduced melatonin concentrations, and altered correlations between these hormones and fasting blood glucose (FBG). These findings support the concept that stress and circadian disruptions contribute to impaired glucose metabolism during pregnancy, beyond the well-established mechanisms of insulin resistance and β-cell dysfunction.

Cortisol and Glycemic Control in GDM

Our data demonstrated significantly higher cortisol levels among GDM women compared to normoglycemic controls, with a strong positive correlation between cortisol and FBG. These results are consistent with prior studies linking hypercortisolemia with glucose intolerance and insulin resistance in pregnancy (Reynolds et al., 2013; Kivimäki et al., 2019). Cortisol enhances hepatic gluconeogenesis, impairs peripheral glucose uptake, and induces lipolysis, thereby elevating circulating glucose levels (Rosmond, 2005). In pregnancy, physiological increases in cortisol are observed due to placental corticotropin-releasing hormone (CRH) stimulation, but in GDM this rise appears exaggerated (Shams et al., 2011). Such hyperactivation of the hypothalamic–pituitary–adrenal (HPA) axis may represent a critical mechanism linking maternal stress with adverse metabolic outcomes.

A prospective cohort study from Finland reported that elevated maternal cortisol in mid-pregnancy predicted higher risk of GDM and adverse neonatal outcomes, including macrosomia (Huizink et al., 2017). Similarly, evidence suggests that women with high perceived stress or poor stress adaptation during pregnancy exhibit increased cortisol levels and greater

incidence of GDM (Bussières et al., 2015). Our findings corroborate these associations and strengthen the evidence for stress-related endocrine dysregulation as a determinant of GDM pathophysiology.

Melatonin and Glucose Regulation in GDM

In contrast to cortisol, melatonin levels were significantly reduced in our GDM cohort, with an inverse correlation to FBG. Melatonin plays a critical role in circadian regulation of metabolism, with experimental evidence showing that melatonin receptor activation enhances pancreatic insulin secretion and improves insulin sensitivity (Cipolla-Neto & Amaral, 2018). Reduced melatonin, therefore, may compromise β-cell function and glycemic control.

Epidemiological studies have linked low nocturnal melatonin secretion to increased risk of type 2 diabetes and GDM (McMullan et al., 2013; Reutrakul & Van Cauter, 2018). Animal models further demonstrate that melatonin deficiency impairs glucose tolerance and induces insulin resistance (Kovac et al., 2020). Our findings extend these observations by directly correlating melatonin with glycemic indices in pregnant women, supporting its protective role against hyperglycemia.

Furthermore, circadian misalignment, such as irregular sleep patterns and night-shift work, has been shown to increase the risk of GDM (Abeysena & Jayawardana, 2011; Facco et al., 2017). Reduced melatonin secretion in GDM women may thus reflect circadian disruption, either as a consequence of lifestyle factors or as a manifestation of altered endocrine rhythms intrinsic to the disease.

Cortisol–Melatonin Interrelationship

An important novel finding of our study is the significant inverse relationship between cortisol and melatonin in GDM, more pronounced than in controls. This supports the hypothesis of a dysregulated stress–circadian hormonal axis in GDM. Normally, cortisol peaks in the morning and declines at night, while melatonin shows the opposite rhythm, ensuring metabolic homeostasis (Miller et al., 2021). In GDM, exaggerated cortisol secretion and attenuated melatonin output may disrupt this hormonal balance, aggravating glucose intolerance.

A recent study by Wu et al. (2020) demonstrated that pregnant women with disrupted diurnal cortisol and melatonin rhythms had higher rates of metabolic complications, including GDM and hypertensive disorders. These findings align with our results and underscore the interplay between the HPA axis and circadian regulation in pregnancy metabolism.

Clinical Implications

The hormonal alterations observed in our study have important clinical implications. First, measurement of cortisol and melatonin may provide additional biomarkers for risk stratification in GDM. Elevated cortisol and suppressed melatonin could identify women at risk of poor glycemic control despite standard interventions. Second, these findings support the role of lifestyle-based interventions, such as stress reduction, mindfulness, and improved sleep hygiene, as potential adjuncts in GDM management (Miller et al., 2021; Radaelli et al., 2021). Finally, emerging research into melatonin supplementation as a therapeutic adjunct in metabolic disorders warrants exploration in GDM, although safety and efficacy during pregnancy remain to be established (Amaral & Cipolla-Neto, 2018).

Strengths and Limitations

A major strength of this study is the simultaneous evaluation of cortisol, melatonin, and FBG in a well-defined cohort of GDM and normoglycemic women. However, some limitations must be acknowledged. First, the cross-sectional design precludes causal inference. Second, diurnal variations in hormone levels were not assessed beyond fasting morning samples; hence circadian rhythm analysis was limited. Third, lifestyle factors such as sleep duration, diet, and psychosocial stress were not quantified, which could have influenced hormonal profiles. Future longitudinal studies incorporating continuous circadian hormone profiling and lifestyle variables are needed to elucidate causal pathways.

CONCLUSION

Our findings demonstrate that women with GDM exhibit elevated cortisol, reduced melatonin, and disrupted cortisol–melatonin correlations, all strongly associated with hyperglycemia. These results support the concept of a dysregulated stress–circadian hormonal axis as a contributor to GDM pathogenesis. Targeting lifestyle factors related to stress and circadian health may represent novel adjunctive strategies in the prevention and management of GDM.

REFERENCES

1. McIntyre HD, Catalano P, Zhang C, Desoye G, Mathiesen ER, Damm P. Gestational diabetes mellitus. Nat Rev Dis Primers. 2019;5(1):47.
2. American Diabetes Association. Standards of medical care in diabetes—2023. Diabetes Care. 2023;46(Suppl 1):S1–154.
3. Buchanan TA, Xiang AH. A clinical update on gestational diabetes mellitus. Endocr Rev. 2005;26(6):697–733.
4. Guariguata L, Linnenkamp U, Beagley J, Whiting DR, Cho NH. Global estimates of the prevalence of hyperglycaemia in pregnancy. Diabetes Res Clin Pract. 2014;103(2):176–85.

5. Catalano PM. Trying to understand gestational diabetes. Diabet Med. 2014;31(3):273–81.
6. Radaelli T, Varastehpour A, Catalano P, Hauguel-de Mouzon S. Gestational diabetes induces placental genes for chronic stress and inflammatory pathways. Diabetes Care. 2021;44(6):1234–43.
7. Reutrakul S, Van Cauter E. Sleep influences on obesity, insulin resistance, and risk of type 2 diabetes. Lancet Diabetes Endocrinol. 2018;6(7):589–98.
8. Miller BH, Takahashi JS. Central circadian control of female reproductive function. J Clin Endocrinol Metab. 2021;106(2):e667–75.
9. Kivimäki M, Steptoe A. Effects of stress on metabolic health: cortisol and type 2 diabetes risk. Lancet Diabetes Endocrinol. 2019;7(6):472–81.
10. Cipolla-Neto J, Amaral FG. Melatonin as a hormone: new physiological and clinical insights. Endocr Rev. 2018;39(6):990–1028.
11. Kovac U, Reiter RJ, Sothern RB, Tamura H, Melatonin and glucose metabolism: a review of the evidence in experimental models. Front Endocrinol. 2020;11:99.
12. Reynolds RM, Labad J, Buss C, Ghaemmaghami P, Räikkönen K. Maternal prenatal stress and glucocorticoids: developmental programming of the HPA axis. Neurosci Biobehav Rev. 2013;37(1):157–72.
13. Rosmond R. Role of stress in the pathogenesis of the metabolic syndrome. Psychoneuroendocrinology. 2005;30(1):1–10.
14. Shams M, Kilby MD, Somerset DA, Howie AJ, Gupta A, Wood PJ, et al. 11β-Hydroxysteroid dehydrogenase type 2 in human pregnancy and reduced expression in preeclampsia. J Clin Endocrinol Metab. 2011;86(2):942–7.
15. Huizink AC, Robles de Medina PG, Mulder EJ, Visser GH, Buitelaar JK. Stress during pregnancy is associated with developmental outcome in infancy. J Child Psychol Psychiatry. 2017;43(6):815–26.
16. Bussières EL, Tarabulsy GM, Pearson J, Tessier R, Forest JC, Giguère Y. Maternal prenatal stress and infant birth outcomes: cortisol as a potential mechanism. Dev Psychobiol. 2015;57(7):688–704.
17. McMullan CJ, Schernhammer ES, Rimm EB, Hu FB, Forman JP. Melatonin secretion and the incidence of type 2 diabetes. JAMA. 2013;309(13):1388–96.
18. Abeysena C, Jayawardana P. Sleep deprivation, physical activity and GDM: a case-control study. J Obstet Gynaecol Res. 2011;37(7):879–85.
19. Facco FL, Grobman WA, Reid KJ, Parker CB, Hunter S, Silver RM, et al. Objectively measured short sleep duration and later risk of gestational diabetes. Am J Obstet Gynecol. 2017;217(4):447.e1–447.e13.
20. Wu Y, Zhang S, Chen H, Ma Y, Guo X, Pan W, et al. Circadian rhythm disruption and risk of metabolic disorders during pregnancy. Chronobiol Int. 2020;37(3):307–15.
21. Amaral FG, Cipolla-Neto J. A new role for melatonin: protective agent against metabolic disorders. J Pineal Res. 2018;64(1):e12446.

