Chapter 2

Physiology of Glucose Metabolism in Pregnancy

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Learning Objectives

- Explain the metabolic adaptations in glucose regulation during pregnancy.
- Describe the hormonal influences on maternal insulin sensitivity and glucose metabolism throughout pregnancy.
- What are the physiological changes in hepatic gluconeogenesis that occur during pregnancy?
- Recognize how pregnancy alters the mass and function of pancreatic β-cells.
- Determine genetic variables, as identified by genome-wide association studies (GWAS), affect glucose metabolism during pregnancy.
- Provide an overview of the metabolomics of gestational glucose metabolism.
- Describe how the gut microbiota affects glucose control in pregnancy.
- Explain the postpartum metabolic alterations.

INTRODUCTION

Pregnancy is a unique physiological state that demands complex adaptations across multiple systems to support fetal development. Among these, metabolic changes-particularly those involving glucose regulation are critical. Early in gestation, increased insulin sensitivity facilitates maternal energy storage, while advancing pregnancy brings a hormonally driven shift toward insulin resistance. This change guarantees the developing fetus a consistent supply of glucose and other nutrients. Gestational diabetes mellitus (GDM), a disorder that has serious consequences for the health of both the mother and the fetus, can arise from the failure of these compensatory systems. In recent years, cutting-edge tools such as genome-wide association studies (GWAS), metabolomics, and microbiome profiling have shed new light on gestational metabolism. These approaches have revealed overlaps between GDM and type 2 diabetes (T2D), identified key metabolic markers, and highlighted the role of the gut microbiome in late pregnancy. Collectively, these revelations enhance our knowledge of normal gestational adaptation and provide possible avenues for more accurate diagnosis and treatment of GDM.

GESTATIONAL GLUCOSE METABOLISM

To maintain a healthy balance between the mother and fetus so as to ensure proper fetal development, maternal adaptation occurs in multiple systems. As far as glucose metabolism is considered, these adaptations occur for adequate shunting of glucose to the developing fetus while maintaining maternal nutrition.

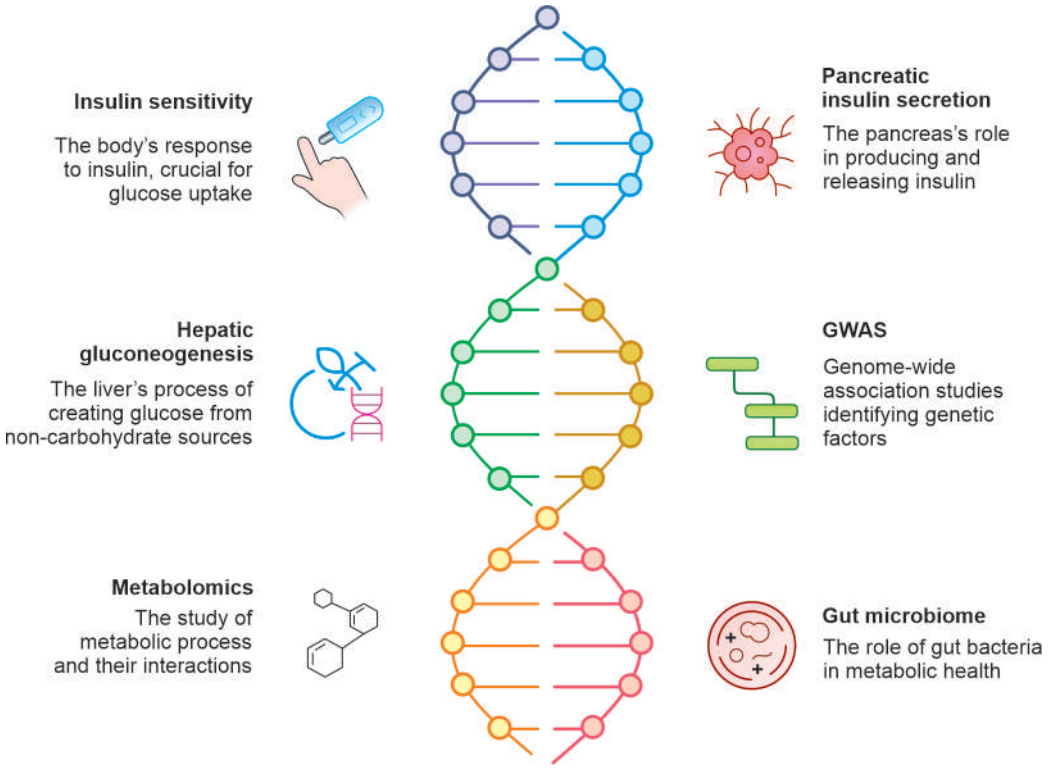

Fig. 2.1: Key processes in gestational glucose metabolism

The chief mechanisms involved in the above process are (Fig. 2.1):

- Insulin sensitivity
- Altered pancreatic β-cell-mediated insulin secretion
- Hepatic gluconeogenesis, adding to this are
- Genome-wide association studies (GWAS)
- Role of metabolomics
- Role of gut microbiome

HORMONAL AND INSULIN SENSITIVITY CHANGES DURING PREGNANCY AND POSTPARTUM

Early Pregnancy (Anabolic Phase)

In early pregnancy, rising levels of estrogen and progesterone, initially from the corpus luteum and later the placenta, promote maternal fat storage to build energy reserves. During this phase, insulin sensitivity in muscle and adipose tissue remains normal or slightly enhanced, ensuring effective glucose uptake. To maintain normoglycemia despite increased metabolic demands, pancreatic β-cell mass and insulin secretion increase significantly. Additionally, leptin levels show a modest rise due to contributions from both maternal adipose tissue and the early placenta. Meanwhile, inflammatory cytokine levels remain low, supporting a favorable immune environment for fetal development **(Fig. 2.2)**.

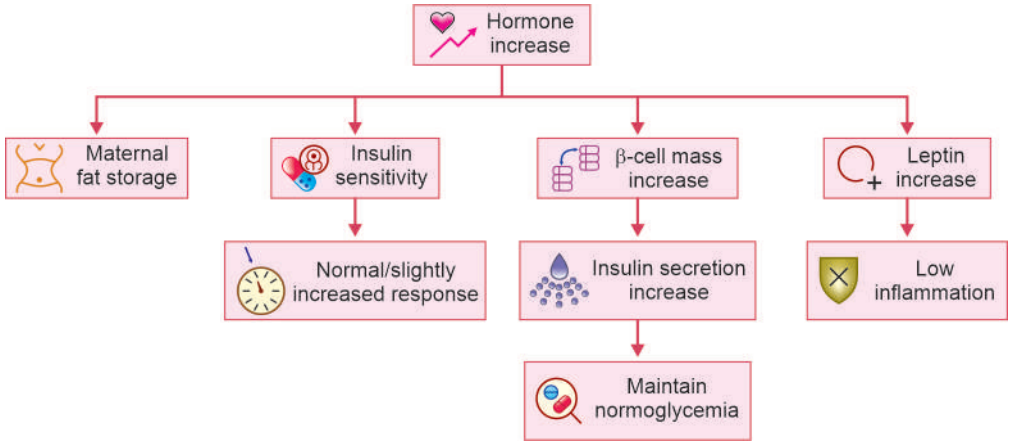

Fig. 2.2: Early pregnancy hormonal and metabolic changes

Mid to Late Pregnancy (Catabolic Phase)

In mid to late pregnancy, the rise in placental hormones such as human placental lactogen (hPL), placental growth hormone, estrogens, and progesterone leads to the development of maternal insulin resistance. This physiological adaptation ensures an adequate glucose supply to the growing fetus. In response, insulin-stimulated glucose uptake in maternal muscle and adipose tissue declines due to reduced GLUT4 activity, while lipolysis increases, releasing free fatty acids (FFA) for maternal energy use. Concurrently, the liver becomes less responsive to insulin's inhibitory effects, resulting in increased hepatic glucose output. Hormonal and inflammatory changes further contribute to insulin resistance: Leptin levels rise, adiponectin decreases, and pro-inflammatory cytokines like TNF-α and IL-6 increases, mainly from placental and adipose sources. To compensate, pancreatic β-cells proliferate and significantly boost insulin secretion, leading to hyperinsulinemia to maintain maternal glucose homeostasis **(Fig. 2.3)**.

At the peak of pregnancy, placental hormones—including human placental lactogen (hPL), growth hormone, estrogen, and progesterone—reach their highest levels, driving maternal insulin resistance to its maximum, with a 50–70% reduction in insulin sensitivity. In muscle and adipose tissue, this severe insulin resistance results in minimal glucose uptake and maximal lipolysis, causing a significant rise in free fatty

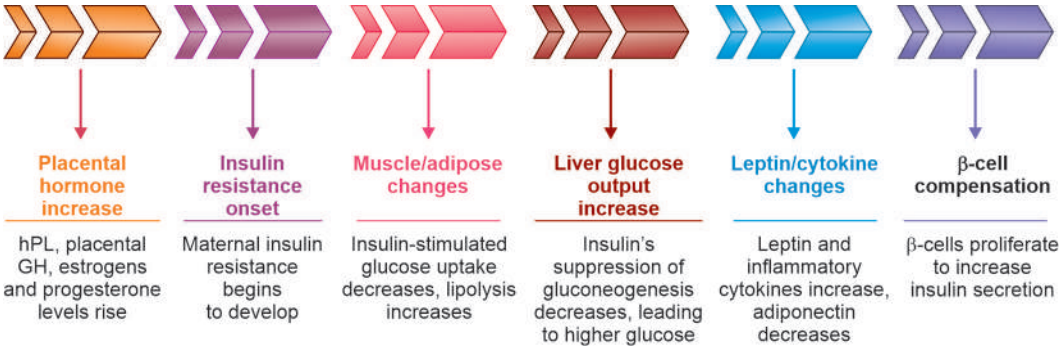

Fig. 2.3 Physiological changes during pregnancy

acids (FFA). The liver exhibits marked insulin resistance as well, leading to increased gluconeogenesis and elevated glucose production. Leptin levels become very high, while pro-inflammatory cytokines such as TNF-α and IL-6 remain elevated, further sustaining insulin resistance. In response, pancreatic β-cells ramp up insulin secretion to 2–3 times normal levels to maintain maternal glucose homeostasis. However, if β-cell compensation fails, this imbalance can lead to the development of gestational diabetes mellitus **(Fig. 2.4)**.

Postpartum

Following delivery, the expulsion of the placenta leads to a rapid decline in placental hormones such as hPL, placental growth hormone, estrogen, and progesterone. As these hormonal drivers of insulin resistance disappear, maternal insulin sensitivity begins to rebound toward pre-pregnancy levels. Consequently, pancreatic β-cell activity decreases, and both insulin secretion and β-cell mass gradually return to baseline. Additionally, levels of leptin and pro-inflammatory cytokines such as TNF-α and IL-6 also fall, further contributing to the resolution of insulin resistance and restoration of normal metabolic function in the postpartum period **(Fig. 2.5)**.

Hepatic Gluconeogenesis in Pregnancy

Gluconeogenesis is the process by which the liver makes new glucose from non-carbohydrate sources (like protein and fat). This helps maintain blood sugar levels, especially during fasting.

Hormonal control of liver glucose production depends upon:

- Insulin normally stops gluconeogenesis, but becomes less effective during pregnancy.
- Placental hormones (e.g. hPL, placental growth hormone): Promote insulin resistance.
- Steroid hormones (e.g. cortisol, progesterone): Increase glucose production and reduce insulin effectiveness.

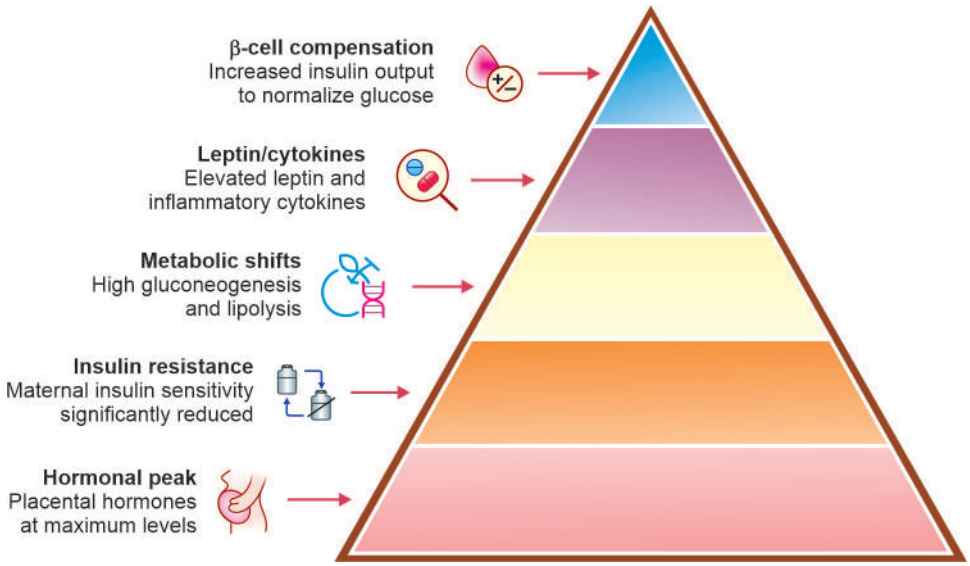

Fig. 2.4: Late pregnancy metabolic changes

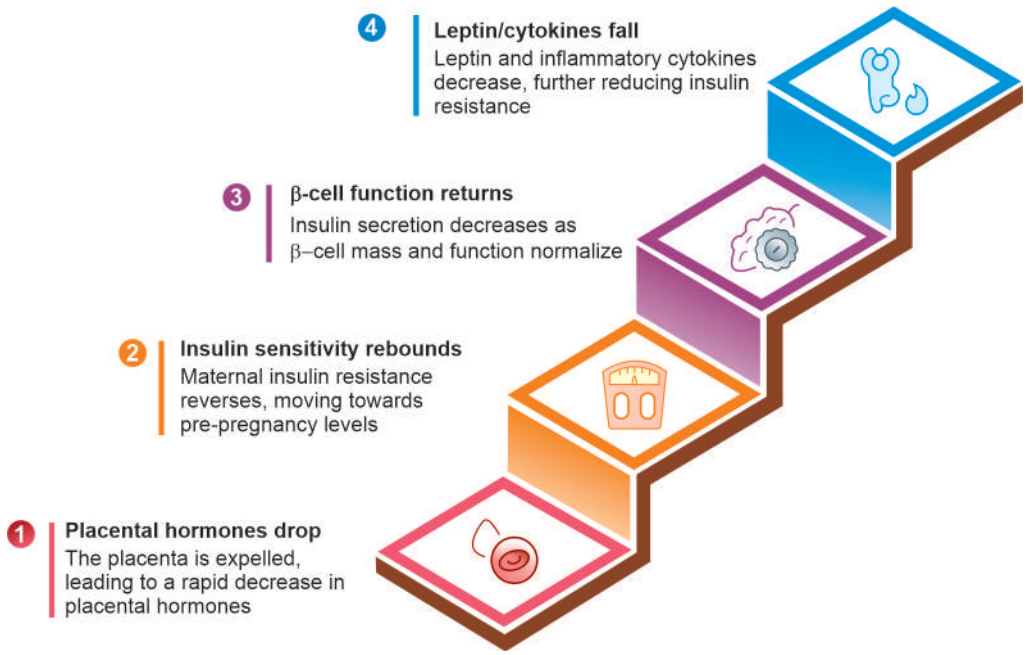

Fig. 2.5: Postpartum metabolic recovery

- Glucagon encourages gluconeogenesis and may be slightly higher in pregnancy.
- Other factors:
  - Adiponectin (which makes the liver sensitive to insulin) drops.
  - Leptin rises, but the mother becomes resistant to it.
  - Thyroid hormones increase slightly, boosting metabolism.

This decrease in insulin sensitivity (by 50–60% in mid to late pregnancy) and the metabolic switch from anabolic in early pregnancy to catabolic in second and third trimester of pregnancy (liver output of glucose increases by ~30%) causes breakdown of fat to make FFA and glucose and ramps up glucose production faster during fasting state called accelerated starvation.

Pancreatic β-cell Adaptations during Pregnancy

Hormonal Triggers for β-cell Adaptation

During pregnancy, elevated levels of placental hormones—particularly prolactin (PRL) and human placental lactogen (hPL)—play a crucial role in adapting maternal β-cell function. These hormones bind to prolactin receptors (PRLR) expressed on pancreatic β-cells, triggering activation of the JAK2/STAT5 signaling pathway. This signaling cascade promotes both β-cell proliferation and enhanced insulin secretion, ensuring that maternal glucose levels remain stable despite the insulin-resistant state induced by other pregnancy hormones. These adaptations are essential for meeting the increased metabolic demands of pregnancy and supporting fetal growth **(Fig. 2.6)**.

β-cell Functional Enhancements

During pregnancy, there are key adaptations in pancreatic β-cell function to meet the increased metabolic demands. One such adaptation is the upregulation of glucokinase

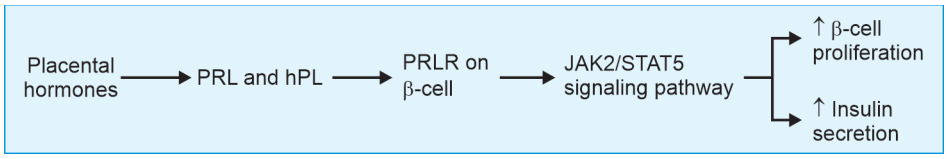

Fig. 2.6: Hormonal activation of β-cells

expression and activity, which enhances glucose sensing and lowers the threshold for glucose-stimulated insulin secretion (GSIS), allowing β-cells to respond more readily to circulating glucose levels. Additionally, serotonin synthesis increases in β-cells, driven by pregnancy-related hormones such as prolactin (PRL), human placental lactogen (hPL), and placental growth hormone (GH-V), which upregulate tryptophan hydroxylase (TPH)—the rate-limiting enzyme in serotonin production. The serotonin produced then acts in an autocrine/paracrine fashion via specific receptors: Htr2b promotes β-cell proliferation, while Htr3a enhances insulin secretion, together contributing to the overall increase in β-cell mass and function during pregnancy **(Fig. 2.7)**.

Epigenetic/Molecular Regulation

During pregnancy, the expression of miR-338-3p—a microRNA that normally suppresses β-cell proliferation—is downregulated. This reduction is regulated in part by elevated estradiol levels. The decrease in miR-338-3p removes its inhibitory effect, thereby permitting the expansion of β-cell mass. This molecular adaptation supports increased insulin production, helping to meet the heightened metabolic demands and maintain glucose homeostasis during pregnancy **(Fig. 2.8)**.

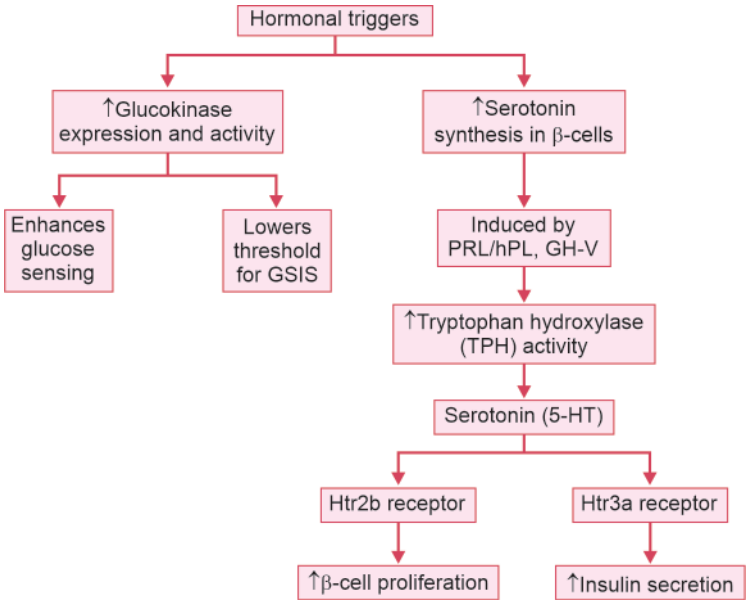

Fig. 2.7: Beta-cell adaptation in early pregnancy

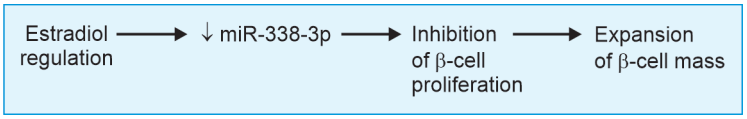

Fig. 2.8: Regulation of β-cell proliferation by miR-338-3p

Outcome of Adaptations

- β-cell mass and number increases
- Insulin secretory capacity increases
- Lowered glucose threshold for insulin release
- Maintains maternal glucose homeostasis during insulin resistance **(Fig. 2.9)**.

Postpartum Changes

After delivery, there is a rapid decline in key pregnancy-related hormones such as prolactin (PRL), human placental lactogen (hPL), placental growth hormone (GH-V), and progesterone. This hormonal withdrawal leads to a reduction in serotonin synthesis and signaling within pancreatic β-cells. Specifically, Htr2b receptor activity—which promotes β-cell proliferation—decreases, while Htr1d receptor activity, associated with growth suppression, increases. As a result, β-cell proliferation declines, and there may be a rise in β-cell apoptosis, contributing to the gradual regression of β-cell mass back to pre-pregnancy levels. This marks the resolution of pregnancy-induced pancreatic adaptations **(Fig. 2.10)**.

GWAS and Glucose Metabolism in Normal Pregnancy

Genome-Wide Association Studies (GWAS) help scientists find genetic factors that influence how the body handles blood sugar (glucose), especially during pregnancy. These studies look across the entire DNA of many people to see which gene variations are linked to certain traits, like higher blood sugar levels.

GWAS studies have discovered certain genes that affect how glucose is handled in pregnancy. Some of these genes are also known from studies on type 2 diabetes (T2D).

Genes Shared with T2D

- Key genes regulate β-cell function, which controls insulin production. GCK acts as a glucose sensor, triggering insulin release. TCF7L2 influences insulin secretion and diabetes risk. MTNR1B affects fasting glucose and β-cell response. KCNQ1 and CDKAL1 impact insulin synthesis and timing. Together, these genes coordinate glucose regulation and insulin balance.

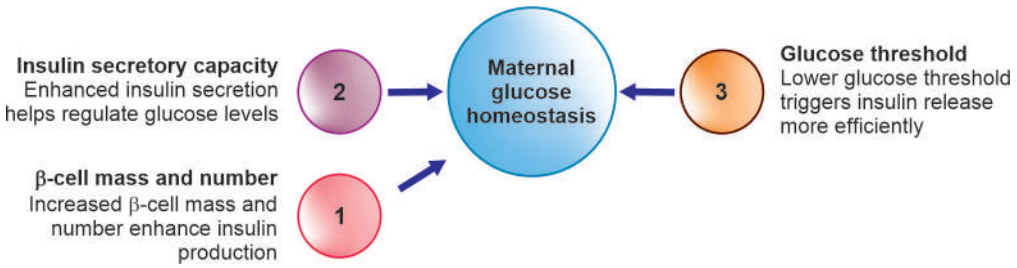

Fig. 2.9: Factors contributing to maternal glucose homeostasis

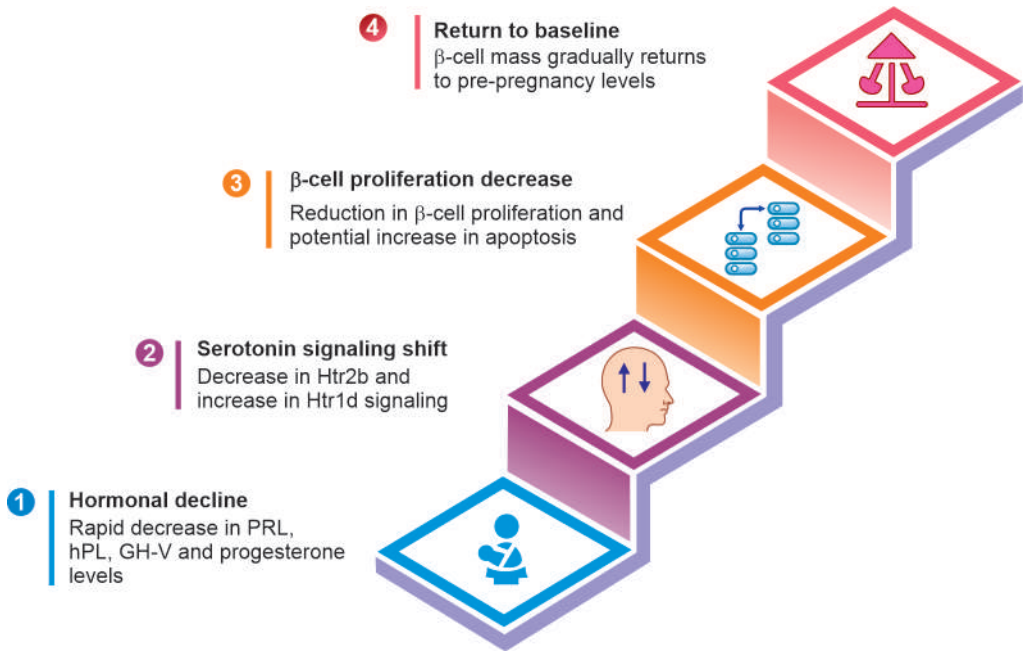

Fig. 2.10: Postpartum hormonal and cellular changes

- Some genes uniquely affect glucose metabolism during pregnancy. HKDC1 influences post-meal glucose levels, while BACE2 is linked to fasting insulin production. These genes play roles in pregnancy-specific β-cell function and glucose regulation, potentially impacting gestational diabetes risk.

It shows that normal pregnancy glucose regulation is controlled by both common and pregnancy-specific genes. It helps explain why some women have higher blood sugar during pregnancy, even if they are otherwise healthy. It gives clues to why some women develop gestational diabetes and others do not. GWAS has helped identify key genes involved in managing blood sugar during normal pregnancy. Some of these genes are the same as those involved in type 2 diabetes, while others are unique to pregnancy. Understanding these genes can improve how we screen, prevent, and manage glucose issues during pregnancy.

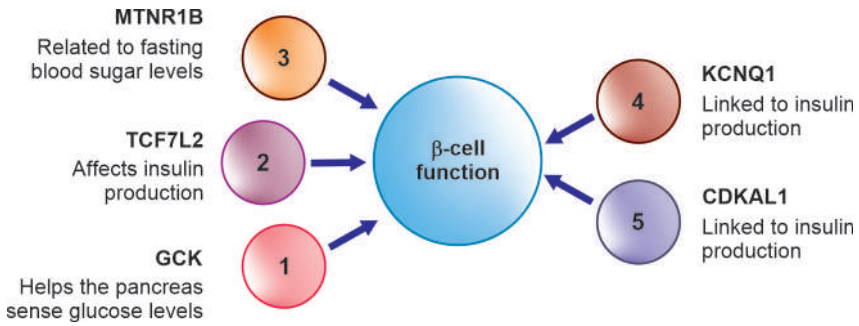

Fig. 2.11: Genetic regulation of beta-cell function

Metabolomics

Metabolomics is the study of all small molecules, called metabolites, within a biological system, such as cells, tissues, or organisms. It aims to identify, quantify, and characterize these metabolites and how they interact, collectively known as the metabolome. This field provides insights into metabolic pathways and their role in health and disease.

In normal pregnancy, metabolomics reveals distinct and dynamic changes in the maternal metabolic profile to support fetal development.

During pregnancy, the body undergoes significant metabolic changes to support both maternal and fetal growth. Lipid metabolism is marked by a progressive increase in triglycerides, especially in the second and third trimesters, to provide energy. Free fatty acids rise due to enhanced lipolysis, particularly in late pregnancy when insulin resistance increases, and cholesterol and phospholipids also elevate to aid in placental and fetal tissue development. Amino acid metabolism shows fluctuating levels of various amino acids like glycine, serine, and alanine. Branched-chain amino acids (BCAAs) such as valine, leucine, and isoleucine may increase in late pregnancy, reflecting altered insulin sensitivity and heightened protein turnover to meet fetal needs. Carbohydrate metabolism is tightly regulated; insulin sensitivity is high in early pregnancy but decreases later. Despite this, blood glucose remains stable due to increased insulin secretion. Ketone bodies like β-hydroxybutyrate and acetone may slightly rise, particularly during fasting or late pregnancy, signaling enhanced fat oxidation. These metabolic adaptations are largely hormone-driven, influenced by human placental lactogen, estrogens, and progesterone, which promote glucose sparing for the fetus and shifts in lipid and protein metabolism. Additionally, the gut microbiome contributes to metabolic regulation through increased production of short-chain fatty acids (SCFAs) early in pregnancy, supporting energy balance and reducing inflammation. In late pregnancy, microbiome changes may lead to higher levels of inflammatory markers and endotoxins, aligning with normal insulin resistance. These metabolomic shifts are physiological and necessary for a healthy pregnancy, but an imbalance may predispose to complications like gestational diabetes mellitus (GDM) **(Fig. 2.12)**.

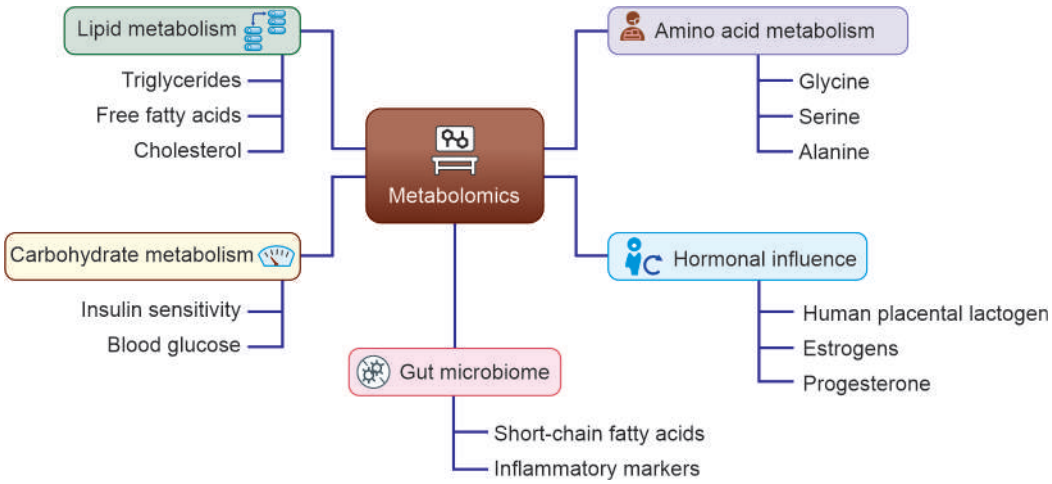

Fig. 2.12: Metabolomic changes during pregnancy

Gut Microbiome in Normal Pregnancy

During pregnancy, the body naturally becomes a bit insulin-resistant to help send more glucose to the growing baby. The gut microbiome (the bacteria in our intestines) helps with this process.

Some gut bacteria play a crucial role in regulating how the body processes sugar and fat. Beneficial bacteria in the gut ferment dietary fiber to produce important substances called short-chain fatty acids (SCFAs). These SCFAs help the body utilize energy efficiently, reduce inflammation, and improve insulin sensitivity, which is vital for maintaining healthy blood sugar levels. When the population of these good bacteria decreases, the production of SCFAs drops, which can lead to increased insulin resistance and contribute to metabolic problems **(Fig. 2.13)**.

Diet and lifestyle matters—certain gut bacteria are essential for managing how the body uses sugar and fat. These good bacteria break down fiber to produce short-chain fatty acids (SCFAs), which play several important roles. SCFAs help the body use energy more effectively, reduce inflammation, and improve how sensitive the body is to insulin. When there are fewer good bacteria, SCFA levels drop, which can increase insulin resistance and negatively affect overall metabolic health.

Probiotics (good bacteria in supplements or foods) may slightly improve insulin sensitivity in pregnancy.

Conclusion

Glucose metabolism in pregnancy undergoes significant changes to support fetal growth, involving a natural progression from increased insulin sensitivity in early pregnancy to marked insulin resistance in late gestation. This shift ensures an adequate glucose supply to the fetus. Maternal adaptations include enhanced pancreatic β-cell function and hepatic gluconeogenesis, while hormonal, genetic, and gut microbiome factors contribute to insulin resistance. When these compensatory mechanisms fail, gestational diabetes mellitus (GDM) may develop. Understanding these complex interactions is

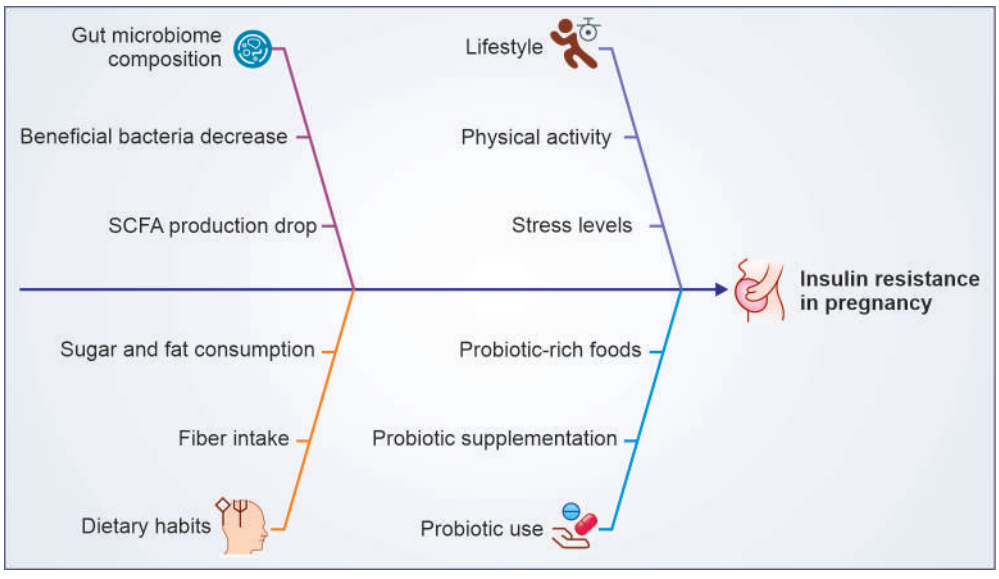

Fig. 2.13: Understanding insulin resistance in pregnancy

vital for early identification and management of GDM, ultimately improving maternal and fetal health outcomes.

Key Points

- Pregnancy presents a unique physiological challenge that requires changes coordinated by placentally and non–placentally derived hormones to prepare the mother for the metabolic stress.
- In recent years, cutting-edge tools such as genome-wide association studies (GWAS), metabolomics, and microbiome profiling have shed new light on gestational metabolism.
- Pancreatic β-cell adaptation is central to maintaining glucose homeostasis in pregnancy.
- Pregnancy is a dynamic shift from the early anabolic to the late catabolic phase.
- Understanding glucose metabolism in pregnancy is crucial for identifying and managing gestational diabetes.

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Long Answer Question (LAQ)

1. Describe the changes in insulin sensitivity and the role of hormonal alterations during pregnancy.

Short Answer Questions (SAQs)

1. How is carbohydrate metabolism regulated across different trimesters of pregnancy?
2. What is the role of gut microbiome-derived short-chain fatty acids in early pregnancy?

Multiple Choice Questions (MCQs)

1. Which of the following best describes glucose metabolism in early pregnancy?
   a. Increased insulin resistance
   b. Enhanced insulin sensitivity and lipogenesis
   c. Decreased insulin secretion
   d. Predominant catabolic state
2. What is the predominant metabolic state in the late third trimester of pregnancy?
   a. Anabolic state with enhanced glucose storage
   b. Increased glucose oxidation
   c. Catabolic state with increased insulin sensitivity
   d. Catabolic state with increased insulin resistance
3. During pregnancy, maternal fasting glucose levels are typically:
   a. Increased due to insulin resistance
   b. Unchanged from pre-pregnancy levels
   c. Slightly decreased due to increased fetal uptake and insulin effect
   d. Increased due to placental glucocorticoid production
4. Which hormone plays a major role in maintaining increased insulin resistance during the second and third trimesters?
   a. Progesterone
   b. Cortisol
   c. Human placental lactogen (hPL)
   d. Oxytocin
5. Why is the fetus considered a "glucose parasite" in pregnancy?
   a. It produces its insulin early in gestation
   b. It actively transports glucose to the mother
   c. It passively receives glucose via facilitated diffusion and cannot perform gluconeogenesis
   d. It stores all maternal glucose in fetal tissues
6. How does maternal lipid metabolism shift in late pregnancy to support fetal glucose needs?
   a. Increased lipolysis and free fatty acid levels in maternal circulation
   b. Increased maternal adipose storage
   c. Decreased ketone body formation
   d. Decreased maternal triglyceride levels
7. The diabetogenic state of pregnancy refers to:
   a. Permanent hyperglycemia post-pregnancy
   b. The physiological increase in insulin sensitivity
   c. The combination of insulin resistance and increased insulin secretion
   d. Inability to produce insulin in late pregnancy
8. In pregnant women, hypoglycemia is more likely to occur:
   a. After meals
   b. During prolonged fasting
   c. During labor
   d. In the early follicular phase

9. Which of the following best describes pancreatic β-cell adaptation during pregnancy?
   a. Decreased β-cell mass and insulin secretion
   b. Increased β-cell apoptosis and reduced function
   c. Increased β-cell proliferation and insulin secretion
   d. Suppressed β-cell function due to estrogen
10. Which of the following factors contributes most significantly to β-cell proliferation during pregnancy?
   a. Glucagon
   b. Prolactin and placental lactogen
   c. Cortisol
   d. Estrogen alone

Answers

1. b	2. d	3. c	4. c	5. c	6. a
7. c	8. b	9. c	10. b		

OSCE Station Scenario

You are a registrar in an antenatal clinic. A pregnant woman (G2P1, 24 weeks of gestation) has just been diagnosed with gestational diabetes mellitus (GDM). She asks, "Why does this happen only during pregnancy?"

Instructions

- Explain the pathophysiology of GDM in simple terms.
- Specifically address pancreatic β-cell adaptation and why it may fail in some women.
- Counsel the patient briefly on the implications for her pregnancy and management options.

Checklist/Marking Scheme (10 marks)

Aspect	*Marks*
• Explains normal insulin resistance in pregnancy (due to placental hormones)	2
• Describes β-cell adaptation (increase in mass/function)	2
• Explains the failure of β-cell compensation in GDM	2
• Discusses implications (e.g. fetal macrosomia, need for monitoring)	2
• Gives a brief management overview (diet, monitoring, and possible insulin)	2
Total	**10**