

## Beyond Metabolism; Fibroblast Growth Factor-21; A New Frontier in Women’s Health and Reproduction

Fibroblast growth factor-21 (FGF21) is a peptide hormone with an endocrine criteria that was initially discovered by a research group in 2000, as a new member of the fibroblast family. It showed unique metabolic regulator properties rather than growth factors as the rest of the FGF family. It is secreted by the hepatic cells (besides other tissues such as the kidney and placenta) in response to fasting and ketone diet, suggesting its potential role in fat and glucose metabolism. FGF21 levels were high among obese individuals, implying resistance to circulating levels similar to insulin resistance in Type II diabetic cases. It gained much attention as a promising therapeutic hormone<sup>[1,2]</sup> and was heavily tested in metabolic disease and obesity research. There were trials to synthesize FGF21 Analog for improved efficiency, bioavailability, and productivity.<sup>[3]</sup> This hormone conducts its role by affecting multiple tissues:<sup>[2]</sup>

- Hepatic cells: It suppress gluconeogenesis and increases glucose uptake by the liver cells
- Pancreatic cells: It optimizes  $\beta$ -cell function and increases insulin hormone secretion
- Fatty cells: It suppress adipocyte-lipolysis and increases glucose uptake.

In addition, FGF 21 has anti-inflammatory actions. Those actions are conducted at the molecular level through upregulating Sirtuin 1, Perilipin expression, and AMP-activated protein kinase.<sup>[2]</sup> A growing body of research discussed its multifaceted roles in obstetrics and gynecology diseases, supporting its role as a prognostic and diagnostic biomarker with potential therapeutic application.<sup>[3]</sup>

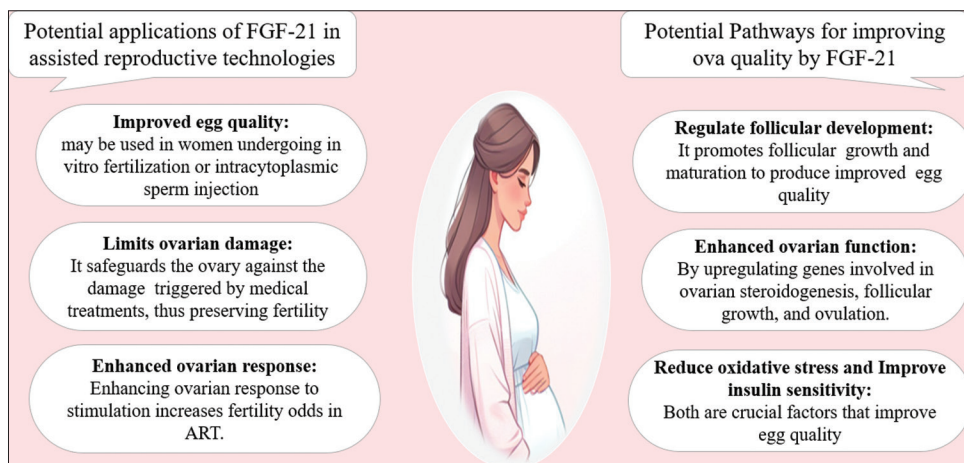
Preeclampsia (PE) is a multisystemic syndrome of high maternal-fetal morbidity; defined by the onset of new hypertension in previously normotensive females after the 20<sup>th</sup> week of pregnancy. FGF21 was found to increase among PE cases and can serve as a reliable predictor for its onset and monitoring of its severity. Moreover, it was linked with fetal growth restriction; a common complication of PE.<sup>[4]</sup>

In gestational diabetes (GDM), serum FGF21 was found to be reduced among pregnant with GDM, suggesting its role in the disease development owing to its regulatory metabolic action. It was tested as a screening and prognostic marker.<sup>[5]</sup>

The cases of polycystic ovarian syndrome (PCOS) are a common endocrinopathy of reproductive age group defined by irregularity of the cycle, hyperandrogenism, and ultrasonic features of polycystic ovaries. FGF21 was increased among PCOS cases due to reduced body sensitivity to its metabolic action. It was proposed as a marker of insulin resistance and other metabolic derangement in affected cases.<sup>[6]</sup>

Recently, FGF-21 has shown promising roles in female fertility, as summarized in Figure 1. Although the exact underlying pathways for improving female fertility are still not well understood, many researchers proposed more than one way:

- Optimized steroidogenesis of ovarian hormones
- Improved energy production by the mitochondria and reduced oxidative stress within the ovary which inversally affects ova quality
- Modulating inflammation positively improves ova quality.<sup>[7]</sup>



**Figure 1:** The main suggested mechanisms by which fibroblast growth factor-21 conducts its favorable effects on female fertility. FGF-21: Fibroblast growth factor-21, ART: Assisted reproductive technology

Despite the promising evidence for the FGF21 application in practice, however, its diagnostic accuracy is hindered by many confounders, including patients' age, obesity, and insulin resistance. Moreover, it can be increased to a diverse cause which limits its specificity.<sup>[8]</sup> As for its therapeutic application, many randomized trials are in progress to determine its optimum dose, duration of action, efficacy, and safety in obesity, diabetes, and nonalcoholic fatty liver disease.<sup>[3]</sup>

In conclusion, FGF21 is a promising biomarker in women's health; however, further research is needed to elucidate its role in female fertility and the mechanism that underlies them. A rigorous evaluation is needed to determine its safety, acceptance, and criterion among diverse populations and diseases for better diagnostic and therapeutic applications. Improved insight into FGF21s role will unlock its potential application for a better reproductive outcome.

### Acknowledgment

The author would appreciate the support of Mustansiriyah University in completing this work.

### Financial support and sponsorship

Nil.

### Conflicts of interest

The author is a member of the editorial team.

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Submitted: 07-Aug-2024 Revised: 28-Aug-2024 Accepted: 05-Sep-2024 Published: 05-Dec-2024

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	<b>DOI:</b> 10.4103/mj.mj_38_24

**How to cite this article:** Nori W. Beyond metabolism; fibroblast growth factor-21; a new frontier in women's health and reproduction. *Mustansiriyah Med J* 2025;24:37-8.