International Journal of Anatomy and Research,
Int J Anat Res 2025, Vol 13(4):9346-53. ISSN 2321-4287
DOI: https://dx.doi.org/10.16965/ijar.2025.236

Original Research Article

Gestational Diabetes Mellitus Affects Placental Iron Transport and Iron Regulatory Proteins

Abdelghany Hassan Abdelghany [1], Ahmed Abdelghany Hassan [1], Sarah Abdelghany Hassan [2], Rania Mohamed Fawzy [1], Rasha Eldeeb [3], Ahmed S. Ahmed [4], Marwa Mahmoud Mady [1,4].

[1] Faculty of medicine, Alexandria University, Alexandria, Egypt.
[2] Faculty of Dentistry, Arab Academy for science, technology and maritime transport, Alamein, Egypt.
[3] Associate Professor of Physiology, Biomedical Sciences Department, College of Medicine, Gulf Medical University (GMU), Ajman, UAE.
[4] Human Anatomy and Embryology, Biomedical Sciences Department, College of Medicine, Gulf Medical University (GMU), Ajman, UAE.

ABSTRACT

Gestational Diabetes Mellitus (GDM) poses significant challenges to maternal-fetal health, yet its impact on placental iron transport remains poorly defined. This study investigates the influence of GDM on the expression and regulation of key placental iron transporters and iron-regulatory proteins. Placental samples from women with GDM and normoglycemic pregnancies were collected at term and analyzed using immunohistochemistry and quantitative PCR to assess expression levels of transferrin receptor (TfR), divalent metal transporter 1 (DMT1), ferroportin (FPN), and ferritin. Our findings reveal that GDM is associated with altered expression patterns of these proteins, particularly downregulation of TfR and DMT1 and dysregulation of FPN, suggesting impaired iron transfer from mother to fetus. Additionally, changes in ferritin levels indicate possible shifts in iron storage dynamics within the placenta. These disruptions may affect fetal iron availability and development, potentially contributing to neonatal iron deficiency and its associated complications. This study highlights the importance of monitoring iron status in pregnancies complicated by GDM. It underscores the need for further investigation into therapeutic strategies to maintain optimal iron transport and homeostasis at the maternal-fetal interface.

KEYWORDS: Gestational Diabetes Mellitus, Placenta, Iron, Ferritin, Transferrin Receptor, Hepcidin.

Corresponding Author: Dr. Marwa Mahmoud Abdelaziz Mady, Associate Professor of Human Anatomy and Embryology, Gulf Medical University, Ajman, UAE **E-Mail:** dr.marwa@gmu.ac.ae

Access this Article online	Journal Information
Quick Response code	**International Journal of Anatomy and Research** ISSN (E) 2321-4287 | ISSN (P) 2321-8967 **https://www.ijmhr.org/ijar.htm** **DOI-Prefix:** https://dx.doi.org/10.16965/ijar
DOI: 10.16965/ijar.2025.236	**Article Information** Received: 27 Jul 2025 Accepted: 12 Nov 2025 Peer Review: 30 Jul 2025 Published (O): 05 Dec 2025 Revised: 15 Oct 2025 Published (P): 05 Dec 2025

INTRODUCTION

The placenta is a unique organ that acts as an interface between the maternal and fetal circulations. It is essential for fetal growth, as it performs important functions such as respiration, excretion, and the exchange of nutrients with the mother. It also plays a vital role in protecting the fetus from the harmful effects of maternal metabolic conditions [1-3].

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy resulting in glucose resistance. It commonly occurs in the second trimester of pregnancy. It is linked to the complications of macrosomia, birth trauma such as increased maternal lacerations and neonatal shoulder dystocia and cardiovascular disease. It also increases the risk of obesity and the development of diabetes mellitus later in life for the mother and baby [4-6].

During pregnancy, maternal and fetal iron requirements increase to support expanding eryth-

-ropoiesis and placental and fetal growth. However, soluble transferrin receptor (sTfR) can be used to assess iron status, and it is markedly elevated in iron deficiency [7]. Several studies have demonstrated a relationship between GDM and elevated serum iron levels, but the pathways linking iron homeostasis during pregnancy to disturbances in glucose metabolism, as well as the role of the placenta in controlling maternofetal iron transfer, are largely unknown [4,8,9].

The machinery in the placenta that handles iron to ensure fetal iron supply is so complicated. Transferrin-bound iron (TBI) from the maternal circulation binds with transferrin receptors (TfR) on the apical membrane of the trophoblastic cells. Then, iron is released into the cytosol. Finally, it is exported to the fetal circulation via ferroportin, the only known iron exporter, which is localized at the basal membrane of trophoblastic cells [8,10-13].

Hepcidin, a small peptide hormone, is secreted in the hepatocytes, macrophages and enterocytes. Multiple studies have proved high maternal serum levels of hepcidin in pregnancies complicated by GDM [4,14]. The placental syncytiotrophoblasts secrete Hepcidin, and there is conûicting evidence regarding its role in downregulating materno-fetal iron transport [8]. Hepcidin binds to ferroportin, triggering its internalisation and degradation, sequestering iron in the placental cell and causing fetal iron deprivation [4,13,15].

This study aimed to explore the placental iron-handling mechanism in GDM and the effects of maternal and placental molecules on placental iron efflux.

MATERIALS AND METHODS

The placentas of 30 women, 15 control and 15 with GDM, were studied after free consent was obtained from the Committee of Ethics in the Faculty of Medicine, Alexandria University. Women with a previous history of diabetes mellitus, hypertension or other chronic diseases were excluded. The maternal ages ranged from 27 to 30 years in the controls and from 28 to 31 years in the GDM group. Fasting blood glucose level was measured after an overnight fast of at least 10 h at 24–28 weeks of gestation.

The diagnosis of GDM was made based on the criteria of the American Diabetes Association (2011) [16].

Blood glucose levels for control cases were within the accepted normal range of 90 to 115 mg/dL throughout gestation, while the GDM women had levels ranging from 120 to 180mg/dL. GDM women were subjected to diet control together with insulin therapy, and their fasting blood glucose was kept in the range of 100 to 135 mg/dL until delivery. Four GDM women had higher fasting blood glucose levels ranging from 140 to 160 mg/dL due to poor diet control and interrupted therapy. The maternal weight during gestation ranged from 63 to 65.5 kg for the control group, and 65.5 to 68 kg for the GDM group. All GDM women were delivered by caesarean section with gestational weeks ranging from 36 to 38 weeks. Ten control women were delivered vaginally, while five were delivered by caesarean section at a gestational age of 36 to 39 weeks. All deliveries were conducted at the Department of Gynaecology and Obstetrics, Faculty of Medicine, Alexandria University. The fetal birth weight ranged from 2.70 to 3.10 kg in the control group, and 3.20 to 3.40 kg in the GDM group. The placental weight ranged from 450 to 480 g in the control group and from 470 to 510 g in the GDM group. The umbilical cords and embryonic membranes were trimmed from the placentas.

1. Biochemical study: maternal serum iron, serum ferritin, sTfR, serum hepcidin and transferrin saturation were measured at term on Cobas c311 and e411 analyzers (Roche Diagnostics International AG; Risch-Rotkreuz, Switzerland) according to the manufacturer's protocols.

2. Histological examination: Paraffin-embedded blocks from formaldehyde-fixed tissues were prepared and cut on a microtome at a thickness of 0.5 µm from each block.

A. Hematoxyline and Eosin: Some sections were stained with hematoxylin and eosin (H&E).

***B.* Tissue Localisation of Iron Ions:** Modified Perl's method was applied to localise iron ions in placental tissues [17]. All slides were treated with 3% (vol/vol) H2O2 in methanol for 60 minutes before staining with Prussian blue

(Santa Cruz Biotechnology Inc.) to control for the activities of endogenous peroxidases and catalases on the substrate. The protocol involves additional steps to intensify the Prussian blue stain by incubating the sections with 3,32 - Diaminobenzidine (DAB) (Vector Laboratories, Inc.; Burlingame, CA) for 30 minutes to produce a permanent brown stain, followed by counterstaining with hematoxylin [17]. A positive reaction was indicated by the presence of a brown colour.

***C.* Immunohistochemistry:** The localisation of placental TfR and hepcidin was conducted using primary polyclonal rabbit IgG antibodies (AntibodyPlus Inc.; Brookline, MA) and Elite Vectastain Rabbit ABC kit (Vector Laboratories Inc.) according to the manufacturer's protocols. The concentrations were 1:100 for TfR and 1:150 for hepcidin. The negative control slides were treated identically to all other slides, except that the primary antibodies were replaced with normal rabbit IgG. The sections were observed with an Optika B-150 (Optika SRL, Ponteranica, Italy) light microscope, and images were captured from 10 random non-overlapping fields for each protein. The images were then quantified in ImageJ as previously described [18,19].

- Sections were examined under Optika B-150 (Optika SRL, Ponteranica, Italy) light microscope.

3. ELISA: ELISA was used to measure the concentrations of hepcidin in placental tissue homogenates using a specific rat kit (Cloud-Clone Corp.; Houston, TX). Glutathione peroxidase (GPX; CUSABIO; Wuhan, China) in placental tissue lysates. Samples were processed in duplicate on an automated ELISA system (Human Diagnostics; Wiesbaden, Germany) according to the manufacturer's guidelines for each kit.

4. Quantitative Reverse Transcription (RT)-PCR: It was used to perform relative quantitative gene expression of rat hepcidin and ferroportin.

5 Statistical analysis: The results were analysed statistically using SPSS 25 (SPSS Inc., Chicago, IL, USA). Mean ± standard deviation (SD) of the two groups was compared using a paired-samples t-test, and the level of significance was accepted as $p<0.05$.

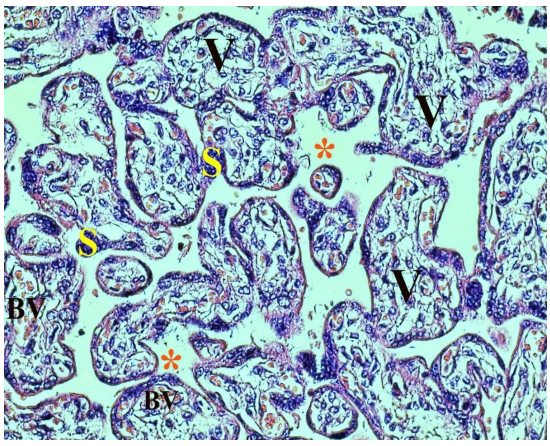

Fig 1(A) H&E-stained section of control placenta showing normal terminal villi (**V**) with thin trophoblastic layers. The syncytiotrophoblast (**S**) displays uniform nuclei and smooth outlines. Fetal blood vessels (**BV**) are visible within the villous core. The intervillous space (*) appears clear and open, reflecting normal maternal–fetal exchange.

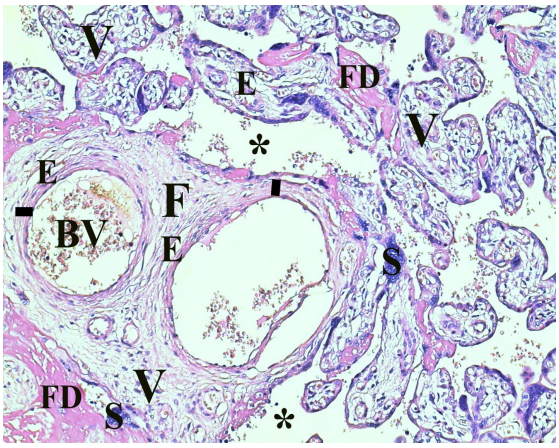

Figure 1 (B) H&E-stained placenta from a GDM case demonstrating villous congestion and thickened trophoblastic surfaces. Syncytiotrophoblast (**S**) appears irregular. Fibrinoid deposition (**FD**) is prominent around the villi, while endothelial cells (**E**) lining enlarged fetal vessels (**BV**) show increased prominence. The intervillous space (*) is partially reduced, indicating impaired perfusion commonly observed in diabetic placentas.

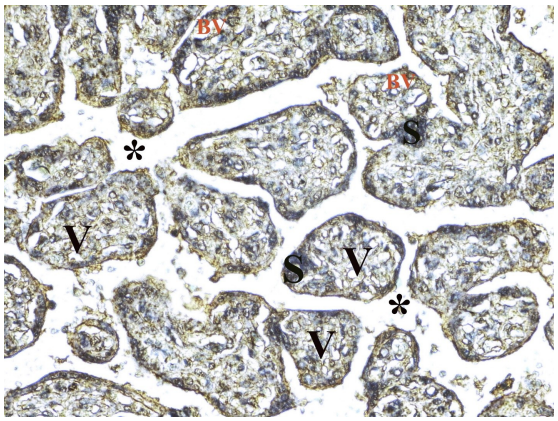

Figure 2 (A) Perl's Prussian blue (DAB-enhanced) stain of control placenta showing minimal iron deposition. Villous structures (**V**) and syncytiotrophoblast (**S**) display only faint brown granules, indicating physiologic iron levels. Fetal vessels (**BV**) appear normal, and maternal intervillous spaces (*) are preserved.

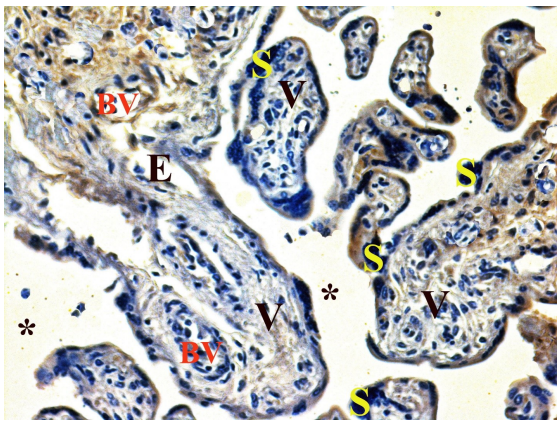

Figure 2 (B) Perl's Prussian blue (DAB-enhanced) stain of GDM placenta revealing increased iron accumulation. Dense brown deposits are present within syncytiotrophoblast (**S**) and around villous surfaces (**V**). Fetal vessels (**BV**) are enlarged, and endothelial lining (**E**) is more prominent. Intervillous spaces (*) appear reduced. These findings reflect altered iron handling in GDM.

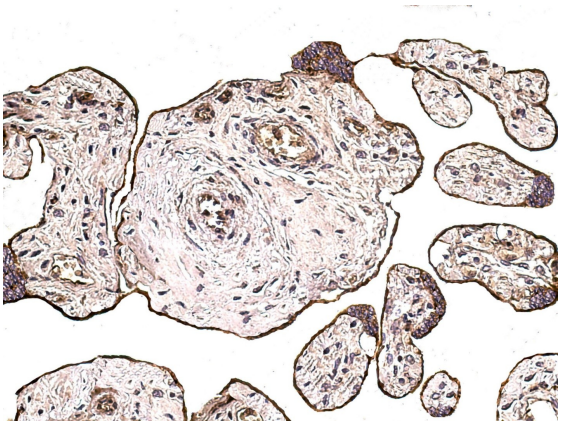

Figure 3 (A) Immunohistochemical localization of transferrin receptor (TfR) in control placenta. Strong, uniform membranous and cytoplasmic immunoreactivity is seen in the syncytiotrophoblast covering the villi, reflecting normal placental iron-uptake activity.

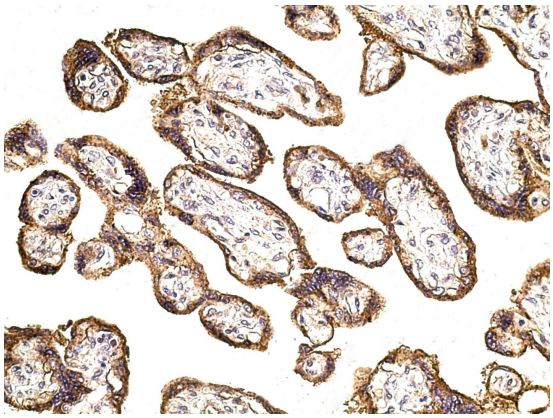

Figure 3 (B) Immunohistochemical localization of transferrin receptor (TfR) in GDM placenta. Immunostaining intensity is clearly reduced compared to control. Syncytiotrophoblast shows weaker positivity over villi, indicating downregulation of TfR expression under hyperglycemic conditions.

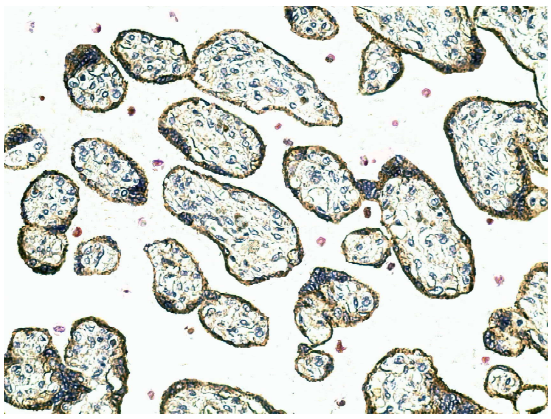

Figure 4 (A) Immunohistochemical expression of hepcidin in control placenta. Mild cytoplasmic staining is detected in syncytiotrophoblasts lining the villi, corresponding to physiologically low hepcidin expression at term to maintain fetal iron supply.

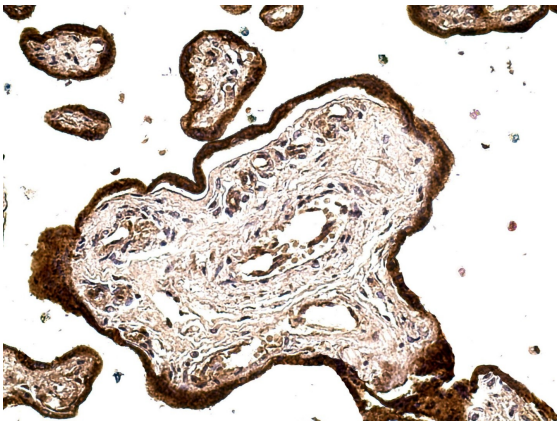

Figure 4 (B) Immunohistochemical expression of hepcidin in GDM placenta: Markedly increased hepcidin staining is observed along syncytiotrophoblast surfaces, especially around large stem villi. This upregulation supports hepcidin-mediated inhibition of ferroportin and impaired placental iron efflux in GDM.

DISCUSSION

Transplacental iron efflux is critical for the appropriate development of the fetus [10]. The pathophysiological association between GDM and elevated maternal serum iron levels, as well as the underlying mechanism of maternofetal iron transfer, remain unclear [4].

Little is known regarding iron homeostasis and iron regulatory proteins in the human placenta that govern transplacental iron flow in GDM. One mechanism proposed by many authors is that GDM shows no significant difference in maternal serum ferritin levels or placental TfR expression, whereas placental hepcidin is reduced, with higher placental ferroportin expression. This increases iron transport into the fetal circulation and iron storage to meet the augmented fetal iron demands late in pregnancy, when iron transfer to the fetus becomes a priority over maternal requirements [4,5,10,20,21].

Ferritin reflects the body's iron stores, and although serum ferritin does not assess circulating iron levels, it may help identify iron overload. The present study showed significantly elevated maternal serum iron and ferritin in GDM. Several studies also demonstrated the same result [5,22,23,24,25]. On the contrary, Yang et al [5] showed no significant difference in serum ferritin in GDM and non-GDM pregnancies. Inconsistencies in serum ferritin levels in the previous studies are attributed to the gestational age at which the studies were conducted. It was proved that serum ferritin is highest near the mid-term and falls with advancing pregnancy till term [5,26].

The exact mechanism underlying high serum ferritin levels and GDM remains unclear. While some authors identified it as a risk factor for GDM, others did not find an association [27-29]. Recent research indicates that iron is strongly associated with GDM due to increased insulin resistance and reduced insulin secretion resulting from pancreatic Beta-cell exhaustion and oxidative injury caused by excess body iron [9-30]. Also, there is increasing recognition that GDM is an inflammatory condition, with the production of inflammatory cytokines leading to elevated serum ferritin levels [5]. Owing to this close relationship some authors have suggested that serum ferritin can predict the development of GDM [5,23-25].

On the contrary, sTfR may be used to assess iron status and is expected to decrease with high serum iron, which explains its close relationship with GDM. Consistent with our results of low sTfR in GDM, Rawal et al. [31] found that sTfR and the ferritin ratio were inversely associated with GDM risk, suggesting that iron overload may contribute to the development of GDM. On the other hand, Yang et al [5] realized elevated sTfR levels in GDM, while Soubasi et al [32] found that sTfR was not related to either high ferritin levels or excess iron stores. However, sTfR is still under consideration for predicting GDM risk [7].

Of no doubt, the apical TfR and basal ferroportin/hepcidin axis of the trophoblastic cells are intensely involved in iron homeostasis and fetal iron availability. The current study showed that GDM exhibits high maternal serum iron associated with downregulation of placental expression of TfR and consequently low placental iron uptake. High maternal serum hepcidin and increased placental hepcidin secretion, evidenced by high expression of mRNA, will negatively affect transplacental iron efflux to the fetus as hepcidin binds and degrades trophoblastic ferroportin, the only known iron exporter.

In vitro studies attempting to mimic hyperglycemic conditions of GDM in the human trophoblast cell line BeWo demonstrated an initial upregulation, followed by a stable downregulation of TfR and ferroportin, with an initial increase, followed by a decrease, in transplacental iron transport[4].

It is of interest that hepcidin is normally downregulated in healthy pregnancy at both the maternal and placental levels to ensure sufficient fetal iron availability [4,10]. Interestingly, the results of the current study support the mechanism that, in GDM, hepcidin production is predominantly regulated at the transcriptional level; hence, the high mRNA expression is to avoid fetal excess iron. Also, GDM is considered a mild inflammatory state characterised by the release of proinflammatory markers, such as hepcidin, consistent with our results [4,14,33].

Little is known about whether maternal or fetal hepcidin affects transplacental iron transport [10]. Sangkhae et al [34] suggested that the fetal compartment has little control over iron transport across the placenta. Many authors observed no correlation between hepcidin concentrations of the cord and placental iron transport, and that low hepcidin expression in the fetal compartment of the placenta did not alter trophoblastic ferroportin expression or iron levels in the placenta or fetal blood [10,365-38]. Moreover, elevated maternal hepcidin levels in GDM may alter placental expression of TfR and ferroportin to prevent excess iron transport to the fetus [4]. On the other hand, maternal iron deficiency wasassociated with increased placental TfR levels, as the placenta guards its own iron stores independently of maternal and fetal iron status, as evidenced by high placental iron concentrations even in the presence of maternal iron deficiency [10,20,34].

These observations, no doubt, should affect placental iron content, as shown in the current

study, with little increase in placental iron in GDM. Unfortunately, few studies have examined placental iron content in GDM. Bake et al [21] revealed increased iron storage in the placenta, while, on the contrary, Zaugg et al [39] showed a reduction in placental iron.

The slight change in placental iron content might not be expected, given the high maternal serum ferritin levels in GDM. This could be explained by reduced placental iron uptake due to downregulation of TfR under hyperglycemic conditions, despite the associated upregulation of hepcidin, which initially overcomes ferroportin expression. This change could be a physiological mechanism to protect the placenta and fetus from oxidative stress (OS) induced by excess iron [4,40].

GDM placenta expresses higher levels of antioxidant enzymes, such as GPX, to maintain redox homeostasis and prevent OS, as shown in the current study and reported by Joo et al. [41]. There is no guarantee that OS results from hyperglycemia or from iron-induced generation of circulating reactive oxygen species (ROS). Studies on GDM human and experimental models showed that antioxidant enzymes, such as GPX, were either upregulated to compensate for OS or downregulated due to the increased ROS levels. These changes depend on the developmental stage and on the response to the gradual increase in ROS levels during pregnancy, which is more pronounced at term [41,42].

The findings of the current study indicate that, in GDM, placental iron uptake and deposition, driven by high fetal iron availability, may be regulated and reduced via iron regulatory proteins as a protective mechanism for the placenta, and fetus against oxidative damage.

CONCLUSION

Iron transport across the placenta and regulation of fetal iron levels are complex processes. GDM is associated with downregulation of TfR and reduced placental iron. Maternal serum hepcidin levels play an essential role in regulating transplacental iron efflux, whereas placental and fetal hepcidin levels do not.

Informed Consent Statement: Informed consent statement was obtained from all subjects included in the study.

Conflicts of Interest: The authors declare no conflicts of interest.

Funding Declaration: No Funding

Author Contributions:

A.H.A.-– Conceptualization; methodology design; sample collection; histological processing; data acquisition; initial manuscript drafting. **A.A.H.-** Biochemical assays; data curation; statistical analysis; contribution to Results section; critical revision of the manuscript. **S.A.H.** – Laboratory assistance; preparation of tissue sections; image documentation; literature review and referencing. **R.M.F.** – Supervision of histological work; interpretation of microscopic findings; validation of methodology; manuscript editing. **R.E.-** Physiological interpretation of findings; contribution to Discussion (maternal metabolic pathways & hepcidin regulation); manuscript review and critical intellectual input. **A.S.A.**– Immunohistochemistry procedures; analysis of protein expression; contribution to figure preparation and legends; data verification. **M.M.M.** – Senior supervision; study conceptual refinement; interpretation of placental morphology and iron regulatory pathways; writing and revising the manuscript; final approval of the version to be published; corresponding author responsibilities.

REFERENCES

[1]. Jadhav A, Khaire A and Joshi S. Exploring the role of oxidative stress, fatty acids and neurotrophins in gestational diabetes mellitus. Growth Factors 2020;38(3-4):226-34. https://doi.org/10.1080/08977194.2021.1895143 PMid:33703982

[2]. Hassan A, Essa TM. Ultrastructure of the placenta in gestational diabetes. Anatomy: An International Journal of Experimental and Clinical anatomy 2016;10(3):159-169. https://doi.org/10.2399/ana.16.019

[3]. Abdelghany AH, Hassan AA, Hassan SA and Fawzy RM. Ultrastructural changes of the placenta in cases of preeclampsia. Magna Scientia Advanced Research and Reviews 2021;30(2):47-60. https://doi.org/10.30574/msarr.2021.3.2.0080

[4]. Zaugg J, Melhem H, Huang X, Wegner M, Baumann M, Surbek D, Körner M, Albrecht C. Gestational diabetes mellitus affects placental iron homeostasis: Mechanism and clinical implications. FASEB J 2020;34(6):7311-29. https://doi.org/10.1096/fj.201903054R PMid:32285992

[5]. Yang A, Zhao J, Lu M, Gu Y, Zhu Y, Chen D and Fu J. Expression of Hepcidin and Ferroportin in the Placenta, and Ferritin and Transferrin Receptor 1 Levels in Maternal and Umbilical Cord Blood in Pregnant Women with and without Gestational Diabetes. Int J Environ Res Pub Health 2016;13:766. https://doi.org/10.3390/ijerph13080766 PMid:27483296 PMCid:PMC4997452

[6]. Abdelghany AH, Eissa TM and Idris S. Study of the ultrastructure of the placenta in gestational diabetes mellitus. Int J Anat Var 2018; 11(1):4-10.

[7]. Zhang C, Rawal S. Dietary iron intake, iron status, and gestational diabetes. Am J Clin Nutr 2017; 106(l):

1672S-80S.
https://doi.org/10.3945/ajcn.117.156034
PMid:29070554 PMCid:PMC5701716

[8]. Principe P , Mukosera GT, Gray-Hutto N, Tugung A, Gheorghe CP and Blood AB. Nitric Oxide Affects Heme Oxygenase-1, Hepcidin, and Transferrin Receptor Expression in the Placenta. Int J Mol Sci 2023;24(6):5887.
https://doi.org/10.3390/ijms24065887
PMid:36982960 PMCid:PMC10056931

[9]. Durrani L, Ejaz S, Tavares LB, Mohyeldin M, Abureesh D, Boorenie M, Khan S. Correlation Between High Serum Ferritin Level and Gestational Diabetes: A Systematic Review. Cureus 2021; 13(10): e18990.
https://doi.org/10.7759/cureus.18990

[10]. McDonald EA, Gundogan F, Olveda RM, Bartnikas TB, Kurtis JD and Friedman JF. Iron transport across the human placenta is regulated by hepcidin. Pediatr Res 2022;92:396–402.
https://doi.org/10.1038/s41390-020-01201-y
PMid:33069164 PMCid:PMC8052381

[11]. Erlandsson L, Masoumi Z, Hansson LR, Hansson SR. The roles of free iron, heme, haemoglobin, and the scavenger proteins haemopexinandalpha-1-microglobulin in preeclampsia and fetal growth restriction. J Intern Med 2021; 290(5):952-968.
https://doi.org/10.1111/joim.13349
PMid:34146434

[12]. Yanatori I, Richardson DR, Toyokuni S, Kishi F. The new role of poly (rC)-binding proteins as iron transport chaperones: Proteins that could couple with inter-organelle interactions to safely traffic iron. Biochem Biophys Acta Gen Subj 2020; 1864(11):129685.
https://doi.org/10.1016/j.bbagen.2020.129685
PMid:32679248

[13]. Lakhal-Littleton S. Advances in understanding the crosstalk between mother and fetus on iron utilization. Semin Hematol 2021;58(3): 153-160.
https://doi.org/10.1053/j.seminhematol.2021.06.003
PMid:34389107

[14]. Anelli GM, Cardellicchio M, Novielli C, Antonazzo P, Mazzocco MI, Cetin I and Mando C. Mitochondrial content and hepcidin are increased in obese pregnant mothers. J Matern Fetal Neonetal Med 2018;31(18):2388-2395.
https://doi.org/10.1080/14767058.2017.1344209
PMid:28625088

[15]. Foot NJ, Dalton HE, Shearwin-whyatt LM, Dorstyn L, Tan SS, Yang B and Kumar S. Regulation of the divalent metal ion transporter DMT1 and iron homeostasis by a ubiquitin-dependent mechanism involving Ndfips and WWP2. Blood. 2016; 112(10): 4268-4276.
https://doi.org/10.1182/blood-2008-04-150953
PMid:18776082

[16]. American Diabetes Association. Standards of medical care in diabetes-2011. Diabetes Care 2011;34:S11-61.
https://doi.org/10.2337/dc11-S011
PMid:21193625 PMCid:PMC3006050
https://doi.org/10.2337/dc11-S011
PMid:21193625 PMCid:PMC3006050

[17]. Asano Y, Meguro R, Odagiri S, Li C, Iwatsuki H, Shoumura K. Visualization of non-heme ferric and ferrous iron by highly sensitive non-heme iron histochemistry in the stress-induced acute gastric lesions in the rat. Histochem Cell Biol. 2006;125:515-25.
https://doi.org/10.1007/s00418-005-0097-6
PMid:16283353

[18]. Nguyen D, Zhou T, Shu J, Mao J. Quantifying chromogen intensity in immunohistochemistry via reciprocal intensity. Cancer InCytes. 2013;2:e.
https://doi.org/10.1038/protex.2013.097

[19]. Shu J, Qiu G, Mohammad I. A semi-automatic image analysis tool for biomarker detection in immunohistochemistry analysis. Qingdao, China: 7th International Conference on Image and Graphics. 2013.
https://doi.org/10.1109/ICIG.2013.197

[20]. Barad A, Guillet R, Pressman EK, Katzman PJ, Miller RK, Darrah TH, O'Brien KO. Placental iron content is lower than previously estimated and is associated with maternal iron status in women at greater risk of gestational iron deficiency and anemia. J Nutr 2022;152(3):737-46.
https://doi.org/10.1093/jn/nxab416
PMid:34875094

[21]. Barke TL, Goldstein JA, Sundermann AC, Reddy AP, Linder JE, Correa H, Velez-Edwards DR, Aronoff DM. Gestational diabetes mellitus is associated with increased CD163 expression and iron storage in the placenta. Am J Reprod Immunol 2018;80:1-13.
https://doi.org/10.1111/aji.13020
PMid:29984475 PMCid:PMC6193471

[22]. Prasad DKV, Sheela P, Kumar AN, Kumar NL, Deedi MK and Madhulatha D. iron levels increased in serum from gestational diabetes mellitus mothers in coastal area of andhra pradesh. J. Diabetes Metab2013;4(5):1-3.
https://doi.org/10.4172/2155- 6156.1000269.

[23]. Lao TT; Chan LY; Tam KF; Ho LF. Maternal hemoglobin and risk of gestational diabetes mellitus in Chinese women. Obstet Gynecol 2002;99(5-1):807-12.
https://doi.org/10.1016/S0029-7844(02)01941-5
PMid:11978291

[24]. Amiri FN, Basirat Z, Omidvar S, Sharbatdaran M, Tilaki KH, Pouramir M. Comparison of the serum iron, ferritin levels and total iron-binding capacity between pregnant women with and without gestational diabetes. J. Nat. Sci. Biol. Med. 2013;4:302-305.
https://doi.org/10.4103/0976-9668.116977
PMid:24082721 PMCid:PMC3783769

[25]. Helin A, Kinnunen TI, Raitanen J, Ahonen S, Virtanen SM, Luoto R. Iron intake, haemoglobin and risk of gestational diabetes: A prospective cohort study. BMJ Open 2012 ;2(5):e001730.
https://doi.org/10.1136/bmjopen-2012-001730
PMid:23015603 PMCid:PMC3467630

[26]. Milman N. Prepartum anaemia: prevention and treatment. Ann Hematol 2008;87(12):949-59.

https://doi.org/10.1007/s00277-008-0518-4 PMid:18641987

[27]. Zein S, Rachidi S, Awada S, Osman M, Al-Hajje A, Shami N, Sharara I, Cheikh-Ali K, Salameh P and Hininger-Favier I. High iron level in early pregnancy increased glucose intolerance. J Trace Elem Med Biol 2015; 30:220-5. https://doi.org/10.1016/j.jtemb.2014.09.004 PMid:25441227

[28]. Behboudi-Gandevani S, Safary K, Moghaddam-Banaem L, Lamyian M, Goshtasebi A, Alian-Moghaddam N. The relationship between maternal serum iron and zinc levels and their nutritional intakes in early pregnancy with gestational diabetes. Biol Trace Elem Res 2013;154(1):7-13. https://doi.org/10.1007/s12011-013-9703-y PMid:23743666

[29]. Sharifi F, Ziaee A, Feizi A, Mousavinasab N, Anjomshoaa A, Mokhtari P. Serum ferritin concentration in gestational diabetes mellitus and risk of subsequent development of early postpartum diabetes mellitus. Diabetes Metab Syndr Obes 2010; 3:413-9. https://doi.org/10.2147/DMSOTT.S15049 PMid:21437111 PMCid:PMC3047976

[30]. Kunutsor SK, Apekey TA, Walley J, Kain K. Ferritin levels and risk of type 2 diabetes mellitus: an updated systematic review and meta-analysis of prospective evidence. Diabetes Metab Res Rev 2013; 29(4):308-18. https://doi.org/10.1002/dmrr.2394 PMid:23381919

[31]. Rawal S, Hinkle SN, Bao W, Zhu Y, Grewal J, Albert PS, Weir NL, Tsai MY, Zhang C. A longitudinal study of iron status during pregnancy and the risk of gestational diabetes: findings from a prospective, multiracial cohort. Diabetologia 2017; 60(2):249-57. https://doi.org/10.1007/s00125-016-4149-3 PMid:27830277 PMCid:PMC6331052

[32]. Soubasi V, Petridou S, Sarafidis K, Tsantali Ch, Diamanti E, Buonocore G, Drossou-Agakidou V: Association of increased maternal ferritin levels with gestational diabetes and intra-uterine growth retardation. Diabetes Metab 2010; 36(1):58-63. https://doi.org/10.1016/j.diabet.2009.06.010 PMid:20074991

[33]. Aydin S, Celik O, Gurates B, Sahin I, Ulas M, Yilmaz M, Kalayci M, Kuloglu T, Catak Z, Aksoy I, Ozercan H and KumruS. Concentrations of preptin, salusins and hepcidins in plasma and milk of lactating women with or without gestational diabetes mellitus. Peptides 2013;49:123-30. https://doi.org/10.1016/j.peptides.2013.09.006 PMid:24060315

34]. Sangkhae V, Fisher AL, Wong S, Koenig MD, Tussing-Humphres L, Chu A, Lelic M, Ganz T and Nemeth E. Effects of maternal iron status on placental and fetal iron homeostasis. J Clin Invest 2020; 130(2):625-40. https://doi.org/10.1172/JCI127341 PMid:31661462 PMCid:PMC6994143

[35]. Sangkhae V, Nemeth E. Placental iron transport: The mechanism and regulatory circuits. Free Radic Biol Med 2019; 133, 254-61. https://doi.org/10.1016/j.freeradbiomed.2018.07.001 PMid:29981833 PMCid:PMC7059975

[36]. Best, C.M.; Pressman, E.K.; Cao, C.; Cooper, E.; Guillet, R.; Yost, O.L.; Galati, J.; Kent, T.R.; O'Brien, K.O. Maternal iron status during pregnancy compared with neonatal iron status better predicts placental iron transporter expression in humans. FASEB J 2016; 30(10):3541-50. https://doi.org/10.1096/fj.201600069R PMid:27402672 PMCid:PMC5024693

[37]. Kämmerer L, Mohammad G, Wolna M, Robbins PA, Lakhal-Littleton S. Fetal liver hepcidin secures iron stores in utero. Blood 2020; 136(13): 1549-57. https://doi.org/10.1182/blood.2019003907 PMid:32542311 PMCid:PMC7515687

[38]. Paradkar PN, Roth JA. Nitric oxide transcriptionally down-regulates speciûc isoforms of divalent metal transporter (DMT1) via NF-kappaB. J Neurochem 2006;96(6);1768-77. https://doi.org/10.1111/j.1471-4159.2006.03702.x PMid:16539692

[39]. Zaugg J, Tello JL, Musial B, Vaughan OR, Fowden AL, Albrecht C and Sferruzzi-Perri AN. Obesogenic diet in pregnancy disrupts placental iron handling and ferroptosis and stress signalling in association with fetal growth alterations. Cell Mol Life Sci 2024; 81(1):151. https://doi.org/10.1007/s00018-024-05192-5 PMid:38526599 PMCid:PMC10963579

[40]. Fuqua BK, Lu Y, Frazer DM, Darshan D, Wilkins SJ, Dunn L, Loguinov AV, Kogan SC, Matak P, Chen H, Dunaief JL, Vulpe CD and Anderson GJ. Severe iron metabolism defects in mice with double knockout of the multicopper ferroxidases hephaestin and ceruloplasmin. Cell Mol Gastroenterol Hepatol 2018; 6(4): 405-27. https://doi.org/10.1016/j.jcmgh.2018.06.006 PMid:30182051 PMCid:PMC6120670

[41]. Joo EH, Kim YR, Kim N, Jung JE, Han SH and Cho HY. Effect of Endogenic and Exogenic Oxidative Stress Triggers on Adverse Pregnancy Outcomes: Preeclampsia, Fetal Growth Restriction, Gestational Diabetes Mellitus and Preterm Birth. Int J Mol Sci 2021; 22(18): 10122. https://doi.org/10.3390/ijms221810122 PMid:34576285 PMCid:PMC8468091

[42]. Hoch D, Gauster M, Hauguel-De Mouzon S and Desoye G. Diabesity-associated oxidative and inflammatory stress signalling in the early human placenta. Mol Aspect Med 2019;66:21-30. https://doi.org/10.1016/j.mam.2018.11.002 PMid:30513311

How to cite this article: Abdelghany Hassan Abdelghany, Ahmed Abdelghany Hassan, Sarah Abdelghany Hassan, Rania Mohamed Fawzy, Rasha Eldeeb, Ahmed S. Ahmed, Marwa Mahmoud Mady. Gestational Diabetes Mellitus Affects Placental Iron Transport and Iron Regulatory Proteins. Int J Anat Res 2025;13(4):9346-9353. **DOI:** 10.16965/ijar.2025.236