Electronic Journal of Education, Social Economics and Technology
Vol. 7, No. 1, (2026), e1445
ISSN 2723-6250 (online)
DOI: https://doi.org/10.33122/ejeset.v7i1.1445

Literature Review

# Prostaglandin E2 and Its Role in Placenta Accreta Spectrum: A Literature Review

**Tin Elasari[1]*, Krisna Murti[2], Erry Gumilar Dachlan[3], Iche Andriyani Liberty[4], Rozi Aditya Aryananda[3]**

[1] Doctorate in Biomedical Science, Faculty of Medicine, Universitas Sriwijaya, Sumatera Selatan, Indonesia
[2] Department of Anatomical Pathology, Faculty of Medicine, Universitas Sriwijaya/Mohammad Hoesin Hospital Palembang
[3] Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga/Dr. Soetomo Regional Hospital Surabaya
[4] Department of Epidemiology and Biostatistics, Faculty of Public Health, Universitas Sriwijaya, Sumatera Selatan, Indonesia
*Corresponding Author: tin_elasari@yahoo.co.id

## ABSTRACT

Placenta accreta spectrum results in significant morbidities. Implantation process is regulated by PGE2 among other factors. This review aimed to discuss the role of PGE2 in the placenta accreta spectrum. Review of literatures searched in PubMed, PubMedCentral, EuropePMC, Wiley, and Science Direct with relevant keywords. Articles found were screened by authors and voted for inclusion. PGE2 is synthesized from arachidonic acid by COX. Increased synthesis of PGE2 results in increased angiogenesis and placental invasion. PGE2 action mainly occurs through the EP1-EP4 as the main receptors of PGE2. Reduced PGE2 receptors expression may results in defective decidualization resulting in poor pregnancy outcomes. Inactivation of PGE2 occurs through HPGD enzyme. Upregulation of HPGD results in lower PGE2 tissue concentration leading to decreased PGE2 activity. Disorders of HPGD expression has been implicated in abnormal implantation in animals. PGE2 synthesis, signaling, and inactivation plays significant role in placental invasion. Defects in any of the processes may lead into placenta accreta spectrum.

**Keywords:** Prostaglandin E2; Prostaglandin Receptor; Hydroxyprostaglandin Dehydrogenase; Placenta Accreta Spectrum

## 1. INTRODUCTION

Placenta accreta spectrum (PAS) is a type of abnormal implantation resulting in increased placental invasion (Jauniaux et al., 2019) Worldwide increasing incidence of cesarean section may lead into increased risk of PAS (Jauniaux et al., 2018, 2019) Riskesdas showed increasing trend of cesarean section, from 9.8% in 2013 to 17.6% in 2018.(Aryananda et al., 2024) Higher incidence of of cesarean section translates into increasing risk of PAS, which in turn leads into increased perinatal death. Considering that 28.7% of all maternal death relates to peripartum hemorrhage, the burden of PAS is not insignificant (Badan Pusat Statistik, 2024; Rahmi et al., 2025).

Patients with PAS is at increased risk of severe postpartum hemorrhage requiring emergency hysterectomy, massive transfusion, and invasive bleeding control measures.(Marcellin et al., 2018) Increased risk of bleeding also carries an increased risk of bladder and ureter injury, disseminated intravascular coagulation, maternal and perinatal death.(Yifru Berhan & Tadesse Urgie, 2020) It is estimated that PAS incidence will increase concurrent with the increase of cesarean section (Morlando et al., 2013)·(Beigi et al., 2012) Implantation is a highly orchestrated event involving several functional and structural remodeling of the uterine tissues. These changes involve several primary mediators, including estrogen and progesterone acting in conjunction to promote immune tolerance and uterine receptivity (Kim & Kim, 2017).

In the light of this view, successful implantation is a concerted effort involving sevaral regulatory factors. Progesterone and estrogen, being the main sex steroid hormones, plays important role in regulation of implantation. Changes in progesterone and estrogen expression after implantation leads into several changes in uterine cavity. Progesterone in particular stimulates endometrial receptivity Kim & Kim, 2017) Nevertheless, implantation, being a pro-inflammatory process, requires inflammatory mediators, including cyclooxygenases (COX) and prostaglandins (PGs). (Norwitz, 2006) InIndeed, luminal epithelial prostaglandin E2 (PGE2) expression is known to increase after implantation, promoting blastocysts attachments and vascular permeability in the site of implantation (Kim & Kim, 2017).

Prostaglandin is a lipid mediator originiaing from the cyclooxygenase-catalyzed metabolism of arachidonic acid. Prostaglandin E2 is known as the most significant type of prostaglandin in the reproductive tissues, where PGE2 has been implicated during the process of ovulation, implantation, angiogenesis, uterine contractility, and vascular homoestasis in pregnancy. In addition of previously mentioned roles, PGE2 is also known to modulate trophoblast differentiation and

migration, endometrial decidualization, and the implantation of the embryo (Norwitz, 2006) Thus, the role of PGE2 in the early stages of trophoblast proliferation is not to be viewed lightly. In this review, we aimed to elaborate the role of PGE2 in the placenta accreta spectrum.

## 2. RESEARCH METHOD

This literature review was conducted through independent searches by the authors on relevant publications in the past 10 years, although older publications were also considered if deemed relevant by the authors. Searches were conducted in PubMed, PubMedCentral, EuropePMC, Wiley, and Science Direct with any combination of the following keywords: "prostaglandin E2"; "PGE2"; "prostaglandin receptor"; "EP receptor"; "HPGD"; "hydroxyprostaglandin dehydrogenase"; "placental invasion"; "implantation". After thorough review of the literatures, we categorized and synthesized relevant literatures into different sections. All prospective papers were included if the full paper was able to be obtained by the author(s) and all authors agreed for inclusions.

## 3. RESULTS AND DISCUSSION

### 3.1 Prostaglandin E2 in Placenta Accreta Spectrum

Prostaglandin (PG) is synthesized from the arachidonic acid by phospholipase A2 from membrane phospholipids. Arachidonic acid is metabolized into different subtypes of PG by prostaglandin-endoperoxide synthases (PTGSs) or cyclooxygenases (COXs). The rate of synthesis of PG is regulated by different mitogens, proinflammatory cytokines, hormones, and growth hormones. PGE2 was synthesized from PGH2 by PGE synthase, located downstream of PG synthesis pathway. Endothelial cells are known to synthesize large quantities of PGs as response for different noxious stimuli related to tissue damage, which in turn allows PGE2 in particular to stimulate angiogenesis through bFGF-mediated pathway.(Simmons et al., 2004; Tamura et al., 2006) In pregnancy, PGE2 is mainly synthesized by the first-trimester trophoblastic villi resulting in a positive feedback loop of invasion and survival of trophoblast.(Biondi et al., 2006)

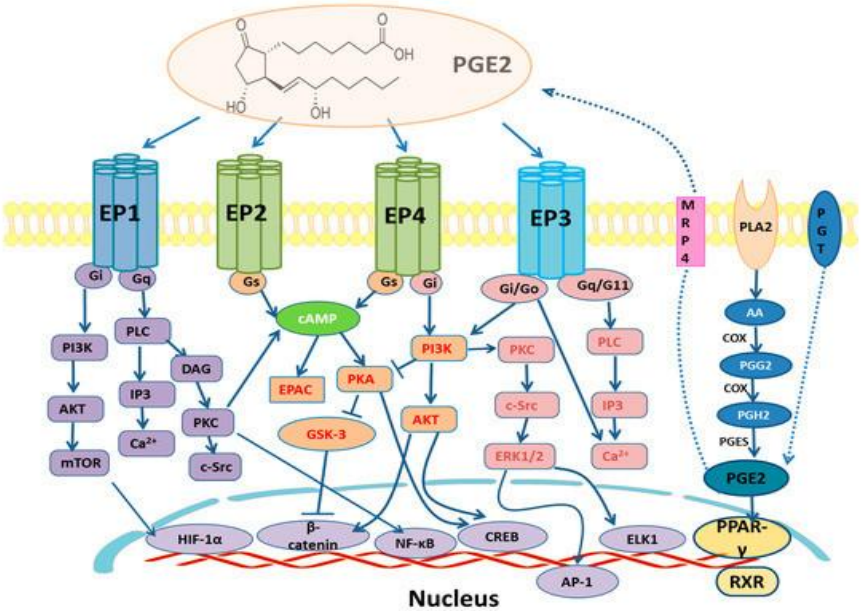


**Figure 1**. PGE2 biosynthesis and signaling pathway.(Ye et al., 2020) PGE2 is synthesized from arachidonic acid (AA) via cyclooxygenase (COX) and prostaglandin E synthase (PGES). PGE2 is then released by MRP4 transporter to form heterodimer complex with membrane-bound EP1, EP2, EP3, and EP4 receptors. Each receptors activate different signaling pathways: **EP1** through Gq and Gi activates PLC, IP3, and $Ca^{2+}$; **EP2** and **EP4** through Gs increase cAMP which activates PKA, EPAC, and ß-catenin; and **EP3** and its several isoforms increase or lower cAMP concentration through Gi or Gq/G11. Activation of downstream pathways, including PI3K/AKT, PKC, ERK1/2, CREB, NF-κB, and AP-1 finally regulates expression of several genes important in proliferation, inflammation, angiogenesis, and differentiation of cells.

The role of PGE2 in placental angiogenesis is widely known. Increased PGE2 secretion is known to stimulate VEGF expression and synergistically interact with bFGF to stimulate proliferation, migration, and differentiation of placental endothelial cells. The significant role of PGE2 in placental invasion is not to be underestimated; particularly important, expression of PGE2 ensures steady availability of oxygenated and nutrient-rich blood in the uteroplacental interface essential for the growth and development of fetus (Simmons et al., 2004; Tamura et al., 2006; Young & Thorburn, 1994).

Prostaglandin E2 (PGE2) is known to intimately regulate implantation and trophoblast proliferation, invasion, angiogenesis, and secretion of pregnancy-related hormones. Thus, it is fair to speculated that dysfunction in PGE2 synthesis may impact placental invasion crucial in the pathogenesis of PAS (Huang et al., 2015; Ye et al., 2018, 2020) Indeed, Peng et al. has highlighted the role of PGE2 through EP4 receptor in the trophoblast function. Their study in HTR-8/SVneo and JEG-3 culture showed that decreased EP4 expression resulted in defective proliferation and cellular viability in addition to increased apoptosis. This significant impact of PGE2-EP4 axis was discovered to occur through the cAMP-PKA-pCREB pathway-related decrease of ß-hCG and progesterone expression. Thus, disruption in PGE2-EP4 axis may result in aberrant control of trophoblast invasion and survival, which in turn may significantly impact pathogenesis of PAS (Peng et al., 2021).

## 3.2 Prostaglandin E2 Receptors in Placenta Accreta Spectrum

Prostaglandin E2 (PGE2) acts through EP1, EP2, EP3, or EP4 receptors in pregnancy. Unfortunately, no specific research of PGE2 and EP receptors in PAS has been conducted and the role of EP receptors are still purely hypothetical. Nevertheless, several evidence has emerged that EP receptors may play significant role in placenta signaling relevant in PAS due to increased evidence of EP receptor imbalances in maternal decidualization (Mirani et al., 2023; Ye et al., 2020).

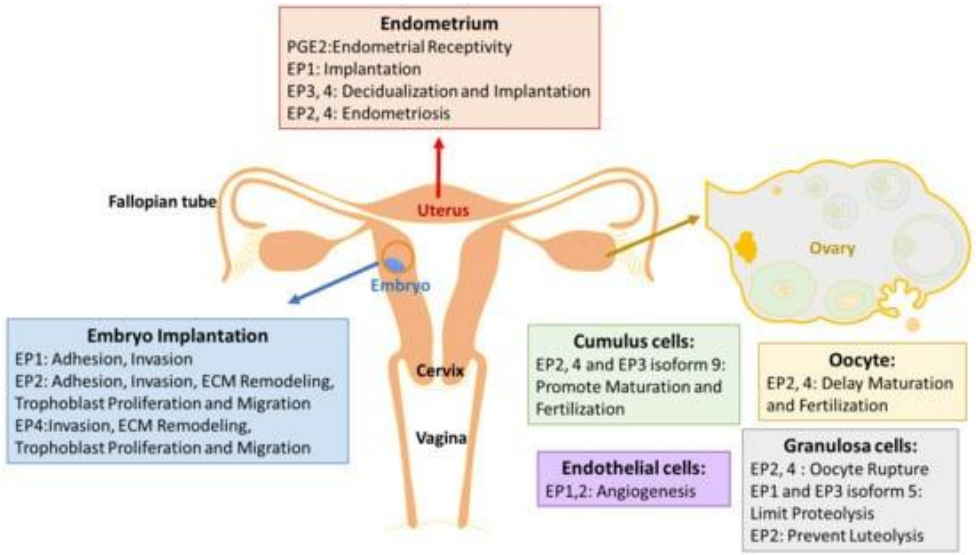


**Figure 2**. Role of prostaglandin receptors in uterus (Ye et al., 2020) Prostaglandin E2 (PGE2) and its receptors significantly regulates wide ranges of reproductive function. Inside endometrium, PGE2 increases endometrial receptiveness and significantly support implantation and decidualization. In addition, PGE2 and its receptors has been implicated in the pathogenesis of endometriosis, another type of placental invasion-related condition in pregnancy. PGE2 role also extends to endometrial tissue, where PGE2 stimulates endometrial receptiveness to support implantation and decidualization in addition to be implicated in the endometriosis. During embryonal implantation, EP1-EP4 receptors mediate adhesion, invasion, extracellular matrix remodeling, and trophoblast migration and proliferation. EP2 and EP4 receptors are known to affect oocyte maturation, ovulation, and fertilization. EP1 and EP3 receptors are known to limit proteolysis and prevent luteolysis in the granulosa cells and oocytes. In cumulus cells, activation of EP2, EP4, and EP3 isoform 9 receptors stimulate oocyte maturation and fertilization. EP1 and EP2 receptors angiogenesis in endothelial cells.

Due to current theory of PAS as a result of failure of regulation of maternal decidualization process, particularly in the uterine scar, it is expected that PGE2 signal dysregulation may affect PAS pathogenesis. It is postulated that disruption of progesterone-related EP2 signaling may result in defective formation of uterine barrier important in prevention of unregulated trophoblast invasion. In addition, EP4 receptor in particular has been implicated in the regulation of extravillous trophoblast signaling pathways significant for proliferation, apoptosis, and secretion of β-hCG and pregnancy-related chemokines. A study in recurrent pregnancy loss has discovered the decreased EP4 expression in the extravillous trophoblast cells from subjects with recurrent pregnancy loss, in addition to another study showing vitro EP4 signaling blockade may result in defective trophoblast proliferation and stimulates apoptosis. Additionally, EP2 and EP4 directly affects local immune response via T-cell and macrophages activities modulation, promoting maternal immune tolerance crucial for the successful pregnancy. Imbalances in EP4 signaling may negatively affect delicate balance of maternal immune tolerance necessary for successful pregnancy (Kandola et al., 2014; Peng et al., 2021; Stadtmauer & Wagner, 2022; Ye et al., 2020).

On the other hand, the role of EP1 and EP3 receptors in PAS are related to the regulation of myometrial contraction and inflammation in lieu of defective decidualization process. Both EP1 and EP3 receptors are known to regulate uterine contraction, where increased EP3 signaling has been disovered in the placentae taken from recurrent pregnancy losses due to its role in the regulation of inflammation microenvironment. Unfortunately, evidence has yet to emerge on the role of EP1 and EP3 in defective decidualization characteristic of PAS (Huang et al., 2015; Ye et al., 2018, 2020).

## 3.3 Hydroxyprostaglandin Dehydrogenase

HPGD (15-hydroxyprostaglandin dehydrogenase) belongs to the family of short-chain alcohol dehydrogenase.(Ensor et al., 1990; Krook et al., 1990) This enzyme is approximately 42-51.5 kDa and has significant role in inactivating PGE1 and PGE2 with the assistance of NADH co-enzyme.(Braithwaite & Jarabak, 1975; Ensor et al., 1990) HPGD enzyme inactivates physiologically-active PGE2 into physiologically-inactive 15-keto-PGE2 with the assistance of $NAD^+$ through hydroxyl group dehydrogenization in the $15^{th}$ carbon position.(Okita & Okita, 1996) The HPGD is coded by *HPGD* gene and known to be upregulated in the endometrial stroma culture when exposed with trophoblast cells;(Popovici et al., 2006) providing evidence for the crucial role of HPGD enzyme in the regulation of PGE2 expression in maternal-fetal interface during the normal pregnancy. The HPGD expression itself is known to come from fetal tissues in lieu of maternal tissues (Erwich & Keirse, 1988).

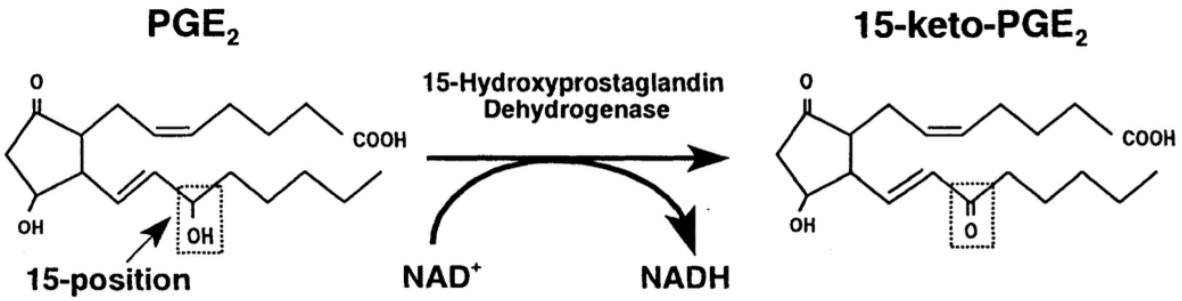


**Figure 3**. Formation of 15-keto-PGE2 from PGE2 by HPGD and $NAD^+$ co-enzyme(Okita & Okita, 1996)

In normal pregnancy, HPGD expression level is closely related to the trophoblast differentiation level. A study of pregnant placental cytotrophoblast cell cultures showed significant increase of HPGD expression in conjunction with the increased cytotrophoblast differentiation into syncytiotrophoblast lineage. In addition, previously mentioned study also showed that changes in both HPGD expression and activity is tightly regulated by the level of cellular cAMP concentration (Lennon et al., 1999) In addition to the trophoblast differentiation phase, HPGD expression is known to be mediated by the tissue concentration of cortisol and progesterone. Indeed, during the study of trophoblast cell culture exposed to cortisol and steroid, it has been discovered that the downregulation of *HPGD* mRNA occurred in line with the increase of cortisol and steroid concentration. Thus, that study provided evidence of the role of cortisol as a competitive inhibitor in the downstream effector of HPGD synthesis in chorion and placenta (Li et al., 2013; Patel et al., 2003). In addition, chorionic HPGD expression is known to be regulated by the expression of progesterone receptor, where the decrease of PR-B receptor expression resulted in the reduced HPGD expression in conjunction with the increase of PR-A receptor expression (Li et al., 2013).

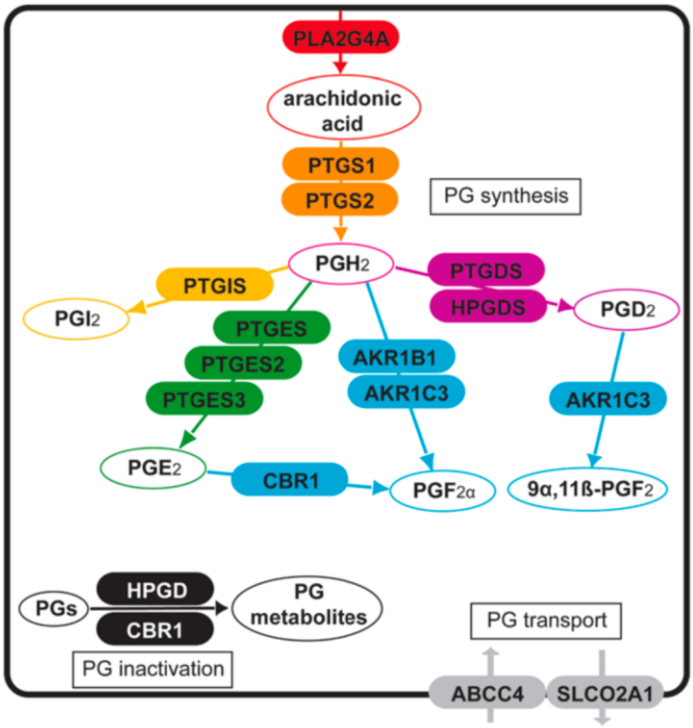


**Figure 4**. Prostaglandin metabolism-related pathways.(Phillips et al., 2014) Figure presented above showed enzymatic components (colored boxes) related to the synthesis of prostaglandin precursors, prostaglandin synthesis, prostaglandin transports, and prostaglandin inactivation in addition to the end-product of the metabolism (oval).

During the process of placental prostaglandin metabolism, HPGD enzyme is known to be related in the maintenance of PGE2 balance by the means of PGE2 inactivation. During the normal pregnancy, HPGD expression is known to be upregulated in the pregnancy not yet in labor, but significantly downregulated near labor. HPGD expression is also differentially regulated, where HPGD expression was found to be higher in the placenta and choriodecidua and lower in the amniotic membrane. Further immunohistochemical study showed that HPGD is also expressed in the extravillous trophoblast and decidua cells in addition to the choriodecidual membrane (Phillips et al., 2014). A study of cow placenta shoed that expression of *HPGD* mRNA was significantly upregulated in the uterine wall during the early stages of pregnancy in comparison with the later stages of pregnancy. In addition, it was discovered that HPGD protein is mainly expressed in the trophoblast and maternal-side epithelilal cells in the maternal-fetal interface. In the uterine tissue itself, highest level of HPGD expression was discovered in the endometrial glands and the uterine lumen epithelial cells, although lesser expression of HPGD could be discovered in the myometrial tissues. Immunohistochemical study provided evidence of downregulation of HPGD expression in the later stages of pregnancy in comparison with the earlier stages of pregnancy (von Hof et al., 2017). In the model of rat pregnancy, it was discovered that HPGD activity in the basal zone is significantly reduced in the mid-pregnancy vs. later stage of pregnancy or early stage of pregnancy. On the other hand, HPGD activity in the labyrinth zone tend to decrease from the early pregnancy and reaches its lowest point at the term placentae (Nagai et al., 1991). Mice model of *Hpgd* gene knockout showed that increase HPGD expression occurred in the $6.5^{th}$ through $8^{th}$ day of pregnancy, whereas the *Hpgd* knockout results in the absorption of the mice embryo due to the increase of PGE2 and PGF2α expression. In addition, *Hpgd* gene knockout also results in the abnormal location of implantation of the embryo (Roizen et al., 2019).

## 4. CONCLUSION

PGE2 synthesis, inactivation, and metabolism significantly affects trophoblast invasion and decidualization process. Disruption in PGE2 signaling or PGE2 inactivation process may significantly increase trophoblast invasion, resulting in increased risk of placenta accreta spectrum disorder. Further studies should elaborate the role of PGE2 in the pathogenesis of placenta accreta spectrum to potentially target this important regulator of implantation.

## ACKNOWLEDGEMENTS

The authors is very grateful for the kind assistance from the colleague in Indonesian College of Obstetricians and Gynecologists, South Sumatra District.

## AUTHOR'S CONTRIBUTIONS

All authors provided equal contribution to this manuscript.

## CONFLICT OF INTEREST

The authors declare no competing interests.

## REFERENCES


Aryananda, R. A., Duvekot, J. J., Van Beekhuizen, H. J., Cininta, N. I., Ariani, G., & Dachlan, E. G. (2024). Transabdominal and transvaginal ultrasound findings help to guide the clinical management of placenta accreta spectrum cases. *Acta Obstetricia et Gynecologica Scandinavica*, *103*(1), 93–102. https://doi.org/10.1111/aogs.14715

Badan Pusat Statistik. (2024). *Profil Kesehatan Ibu dan Anak 2024* (Vol. 10).

Beigi, R., Phillips Heine, ; R, Silver, R. M., & Wax, J. R. (2012). *Placenta Accreta Spectrum*.

Biondi, C., Ferretti, M. E., Pavan, B., Lunghi, L., Gravina, B., Nicoloso, M. S., Vesce, F., & Baldassarre, G. (2006). Prostaglandin E2 Inhibits Proliferation and Migration of HTR-8/SVneo Cells, a Human Trophoblast-derived Cell Line. *Placenta*, *27*(6–7), 592–601. https://doi.org/10.1016/j.placenta.2005.07.009

Braithwaite, S., & Jarabak, J. (1975). Studies on a 15-hydroxyprostaglandin dehydrogenase from human placenta. Purification and partial characterization. *Journal of Biological Chemistry*, *250*(6), 2315–2318. https://doi.org/10.1016/S0021-9258(19)41718-3

Ensor, C. M., Yang, J. Y., Okita, R. T., & Tai, H. H. (1990). Cloning and sequence analysis of the cDNA for human placental NAD+-dependent 15-hydroxyprostaglandin dehydrogenase. *Journal of Biological Chemistry*, *265*(25), 14888–14891. https://doi.org/10.1016/s0021-9258(18)77199-8

Erwich, J. J. H. M., & Keirse, M. J. N. C. (1988). Human placental 15-hydroxy-prostaglandin dehydrogenase activity is under fetal genetic control. *Prostaglandins*, *35*(1), 123–131. https://doi.org/10.1016/0090-6980(88)90280-8

Huang, N., Liu, B., Dong, Z., Mao, W., Zhang, N., Li, C., & Cao, J. (2015). Prostanoid receptors EP2, EP4, and FP are regulated by estradiol in bovine oviductal smooth muscle. *Prostaglandins and Other Lipid Mediators*, *121*, 207–217. https://doi.org/10.1016/j.prostaglandins.2015.08.002

Jauniaux, E., Bunce, C., Grønbeck, L., & Langhoff-Roos, J. (2019). Prevalence and main outcomes of placenta accreta spectrum: a systematic review and meta-analysis. *American Journal of Obstetrics and Gynecology*, *221*(3), 208–218. https://doi.org/10.1016/j.ajog.2019.01.233

Jauniaux, E., Collins, S., & Burton, G. J. (2018). Placenta accreta spectrum: pathophysiology and evidence-based anatomy for prenatal ultrasound imaging. *American Journal of Obstetrics and Gynecology*, *218*(1), 75–87. https://doi.org/10.1016/j.ajog.2017.05.067

Kandola, M. K., Sykes, L., Lee, Y. S., Johnson, M. R., Hanyaloglu, A. C., & Bennett, P. R. (2014). EP2 receptor activates dual g protein signaling pathways that mediate contrasting proinflammatory and relaxatory responses in term pregnant human myometrium. *Endocrinology*, *155*(2), 605–617. https://doi.org/10.1210/en.2013-1761

Kim, S.-M., & Kim, J.-S. (2017). A Review of Mechanisms of Implantation. *Development & Reproduction*, *21*(4), 351–359. https://doi.org/10.12717/DR.2017.21.4.351

Krook, M., Marekov, L., & Jörnvall, H. (1990). Purification and structural characterization of placental NAD+-linked 15-hydroxyprostaglandin dehydrogenase. The primary structure reveals the enzyme to belong to the short-chain alcohol dehydrogenase family. *Biochemistry*, *29*(3), 738–743. https://doi.org/10.1021/bi00455a021

Lennon, C., Carlsona, M. G., Nelson, D. M., & Sadovsky, Y. (1999). In vitro modulation of the expression of 15-hydroxy-prostaglandin dehydrogenase by trophoblast differentiation. *American Journal of Obstetrics and Gynecology*, *180*(3), 690–695. https://doi.org/10.1016/S0002-9378(99)70274-7

Li, Y., He, P., Sun, Q., Liu, J., Gao, L., You, X., Gu, H., & Ni, X. (2013). Reduced Expression of 15-Hydroxy Prostaglandin Dehydrogenase in Chorion during Labor Is Associated with Decreased PRB and Increased PRA and GR Expression. *The American Journal of Pathology*, *182*(5), 1585–1594. https://doi.org/10.1016/j.ajpath.2013.01.033

Marcellin, L., Delorme, P., Bonnet, M. P., Grange, G., Kayem, G., Tsatsaris, V., & Goffinet, F. (2018). Placenta percreta is associated with more frequent severe maternal morbidity than placenta accreta. *American Journal of Obstetrics and*

*Gynecology*, *219*(2), 193.e1-193.e9. https://doi.org/10.1016/j.ajog.2018.04.049

Mirani, P., Lestari, P. M., Murti, K., Liberty, I. A., Andrina, H., Kesty, C., & Stevanny, B. (2023). Placenta accreta spectrum disorder: An updated literature review. *Jurnal Kedokteran Dan Kesehatan Indonesia*. https://doi.org/10.20885/jkki.vol14.iss3.art15

Morlando, M., Sarno, L., Napolitano, R., Capone, A., Tessitore, G., Maruotti, G. M., & Martinelli, P. (2013). Placenta accreta: incidence and risk factors in an area with a particularly high rate of cesarean section. *Acta Obstetricia et Gynecologica Scandinavica*, *92*(4), 457–460. https://doi.org/10.1111/aogs.12080

Nagai, K., Nabekura, H., Mibe, M., Ohshige, T., & Mori, N. (1991). Prostaglandin dehydrogenase activity in placenta and in maternal lung, kidney, and gastric mucosa during rat pregnancy. *Molecular and Cellular Endocrinology*, *80*(1–3), 153–163. https://doi.org/10.1016/0303-7207(91)90152-I

Norwitz, E. R. (2006). Defective implantation and placentation: laying the blueprint for pregnancy complications. *Reproductive BioMedicine Online*, *13*(4), 591–599. https://doi.org/10.1016/S1472-6483(10)60649-9

Okita, R. T., & Okita, J. R. (1996). Prostaglandin-metabolizing enzymes during pregnancy: Characterization of NAD+-dependent prostaglandin dehydrogenase, carbonyl reductase, and cytochrome P450-dependent prostaglandin omega-hydroxylase. In *Critical Reviews in Biochemistry and Molecular Biology* (Vol. 31, Number 2, pp. 101–126). Informa Healthcare. https://doi.org/10.3109/10409239609106581

Patel, F. A., Funder, J. W., & Challis, J. R. G. (2003). Mechanism of Cortisol/Progesterone Antagonism in the Regulation of 15-Hydroxyprostaglandin Dehydrogenase Activity and Messenger Ribonucleic Acid Levels in Human Chorion and Placental Trophoblast Cells at Term. *The Journal of Clinical Endocrinology & Metabolism*, *88*(6), 2922–2933. https://doi.org/10.1210/jc.2002-021710

Peng, L., Chelariu-raicu, A., Ye, Y., Ma, Z., Yang, H., Ishikawa-ankerhold, H., Rahmeh, M., Mahner, S., Jeschke, U., & von Schönfeldt, V. (2021). Prostaglandin E2 receptor 4 (EP4) affects trophoblast functions via activating the cAMP-PKA-pCREB signaling pathway at the maternal–fetal interface in unexplained recurrent miscarriage. *International Journal of Molecular Sciences*, *22*(17). https://doi.org/10.3390/ijms22179134

Phillips, R. J., Fortier, M. A., & López Bernal, A. (2014). Prostaglandin pathway gene expression in human placenta, amnion and choriodecidua is differentially affected by preterm and term labour and by uterine inflammation. *BMC Pregnancy and Childbirth*, *14*(1). https://doi.org/10.1186/1471-2393-14-241

Popovici, R. M., Betzler, N. K., Krause, M. S., Luo, M., Jauckus, J., Germeyer, A., Bloethner, S., Schlotterer, A., Kumar, R., Strowitzki, T., & Von Wolff, M. (2006). Gene expression profiling of human endometrial-trophoblast interaction in a coculture model. *Endocrinology*, *147*(12), 5662–5675. https://doi.org/10.1210/en.2006-0916

Rahmi, J., Noviana Sari, Y., Aprilianingrum, L., Sri Muzdalifah, R., Assa, A., Kusoemo, diah, Tinggi Ilmu Kesehatan Widya Dharma Husada Tangerag, S., No, J., Barat, P., Pamulang, K., & Tangerang Selatan, K. (2025). Deteksi Dini Faktor Resiko Dan Intervensi Melalui Pelayanan Anc Untuk Mencegah Terjadinya Kekurangan Energi Kronis (Kek) Early Detection Of Risk Factors And Intervention Through Antenatal Care (Anc) To Prevent Chronic Energy Deficiency (Ced). In *Jurnal Abdi Masyarakat* (Vol. 6, Number 1).

Roizen, J. D., Asada, M., Tong, M., Tai, H. H., & Muglia, L. J. (2019). Early pregnancy loss in 15-hydroxyprostaglandin dehydrogenase knockout (15-HPGD−/−) mice due to requirement for embryo 15-HPGD activity. *Scientific Reports*, *9*(1). https://doi.org/10.1038/s41598-019-54064-7

Simmons, D. L., Botting, R. M., & Hla, T. (2004). Cyclooxygenase Isozymes: The Biology of Prostaglandin Synthesis and Inhibition. *Pharmacological Reviews*, *56*(3), 387–437. https://doi.org/10.1124/pr.56.3.3

Stadtmauer, D. J., & Wagner, G. P. (2022). Single-cell analysis of prostaglandin E2-induced human decidual cell in vitro differentiation: a minimal ancestral deciduogenic signal. *Biology of Reproduction*, *106*(1), 155–172. https://doi.org/10.1093/biolre/ioab183

Tamura, K., Sakurai, T., & Kogo, H. (2006). Relationship between prostaglandin E2 and vascular endothelial growth factor (VEGF) in angiogenesis in human vascular endothelial cells. *Vascular Pharmacology*, *44*(6), 411–416. https://doi.org/10.1016/j.vph.2006.02.009

von Hof, J., Sprekeler, N., Schuler, G., Boos, A., & Kowalewski, M. P. (2017). Uterine and placental expression of HPGD in cows during pregnancy and release of fetal membranes. *Prostaglandins and Other Lipid Mediators*, *128–129*, 17–26. https://doi.org/10.1016/j.prostaglandins.2016.12.003

Ye, Y., Lin, P., Zhu, J., Jeschke, U., & von Schönfeldt, V. (2020). Multiple Roles of Prostaglandin E2 Receptors in Female Reproduction †. *Endocrines*, *1*(1), 22–34. https://doi.org/10.3390/endocrines1010003

Ye, Y., Vattai, A., Ditsch, N., Kuhn, C., Rahmeh, M., Mahner, S., Ripphahn, M., Immler, R., Sperandio, M., Jeschke, U., & Von Schönfeldt, V. (2018). Prostaglandin E2 receptor 3 signaling is induced in placentas with unexplained recurrent pregnancy losses. *Endocrine Connections*, *7*(5), 749–761. https://doi.org/10.1530/EC-18-0106

Yifru Berhan, & Tadesse Urgie. (2020). A Literature Review of Placenta Accreta Spectrum Disorder: The Place of Expectant Management in Ethiopian Setup. *Ethiopian Journal of Health Sciences*, *30*(2). https://doi.org/10.4314/ejhs.v30i2.16

Young, I. R., & Thorburn, G. D. (1994). Prostaglandin E $_2$ , Fetal Maturation and Ovine Parturition. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, *34*(3), 342–346. https://doi.org/10.1111/j.1479-828X.1994.tb01086.x