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MATERNAL-FETAL MEDICINE

Enhanced expression of αVβ3 integrin in villus and extravillous trophoblasts of placenta accreta

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Abstract

Background Placenta accreta is one of the most serious complications in obstetrics and gynecology. Villous trophoblasts (VT) and extravillous trophoblasts (EVT) play a central role in normal placentation. Placenta accreta is characterized by abnormal invasion of EVT cells through the uterine layers, due to changes in several parameters, including adhesion proteins. Although αvβ3 integrin is a central adhesion molecule, participating in multiple invasive pathological conditions including cancer, data on placenta accreta are lacking.

Objective To study the expression pattern of αvβ3 integrin in placenta accreta in comparison with normal placentas.

Study design We collected tissue samples from placentas defined as percreta, the most severe presentation of placenta accreta and from normal control placentas ($n = 10$ each). The samples underwent protein extractions for analyses of αvβ3 expression by Western blots (WB) and a parallel tissue assessment by immunohistochemistry (IHC).

Results WB results indicated significantly elevated αvβ3 integrin expression in the percreta samples compared to normal placentas. These elevated levels were mainly contributed by EVT cells, as demonstrated by IHC. αvβ3 integrin demonstrated a classical membranal expression in the VT cells, whereas a uniformly distributed expression was documented in the EVT cells. These patterns of the αvβ3 integrin localization were similar in both accreta and normal placental samples.

Conclusions Enhanced αvβ3 integrin expression, mainly in extra villous trophoblasts of placenta percreta, implies for a role of this adhesion molecule in pathological placentation.

Outlines

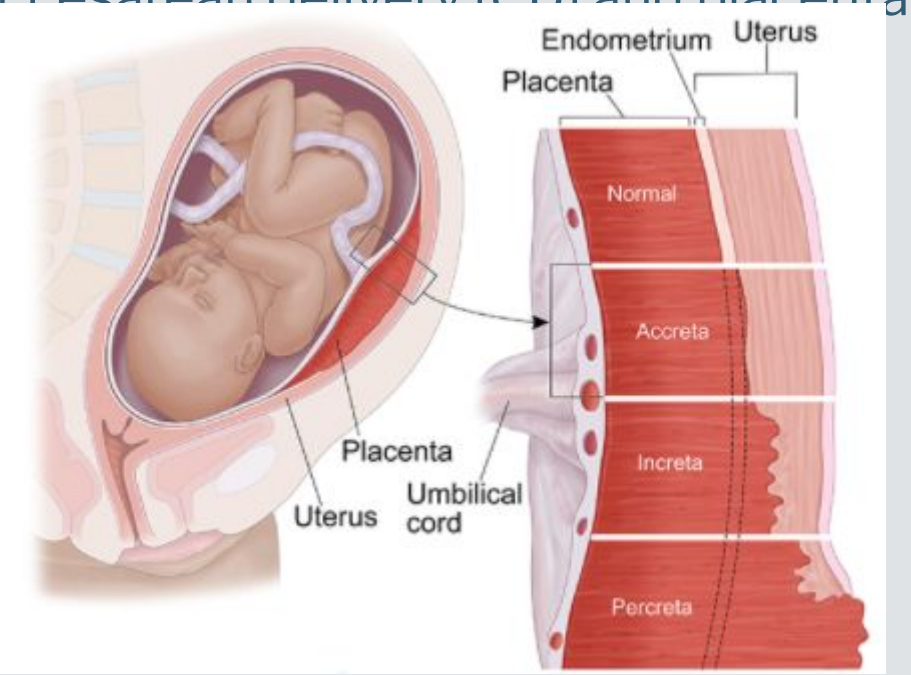
- Article and journal characteristics
- Introduction
- Materials and methods
- Results
- Discussion
- Conclusion
- Questions for discussion

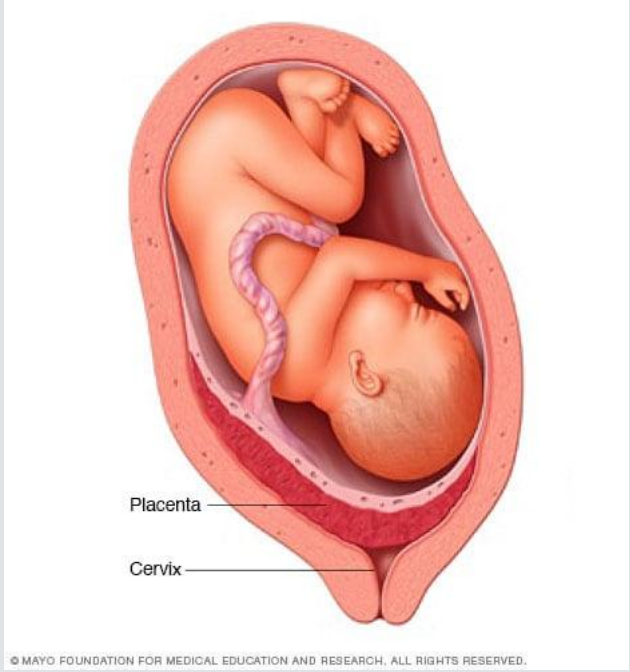
Article and journal characteristics

- Published in ***Archives of Gynecology and Obstetrics*** (Q2, h-index of 68, IF = 2.344, Open access journal) on 28 October 2020.
- Original research.
- Retrospective study.
- 20 female patients were devided into 2 groups based on their placental status (n=10 of placenta accreta; n=10 normal control placentas).
- Tissue samples were collected from January 2015 through April 2019.
- References: 44 articles

Introduction

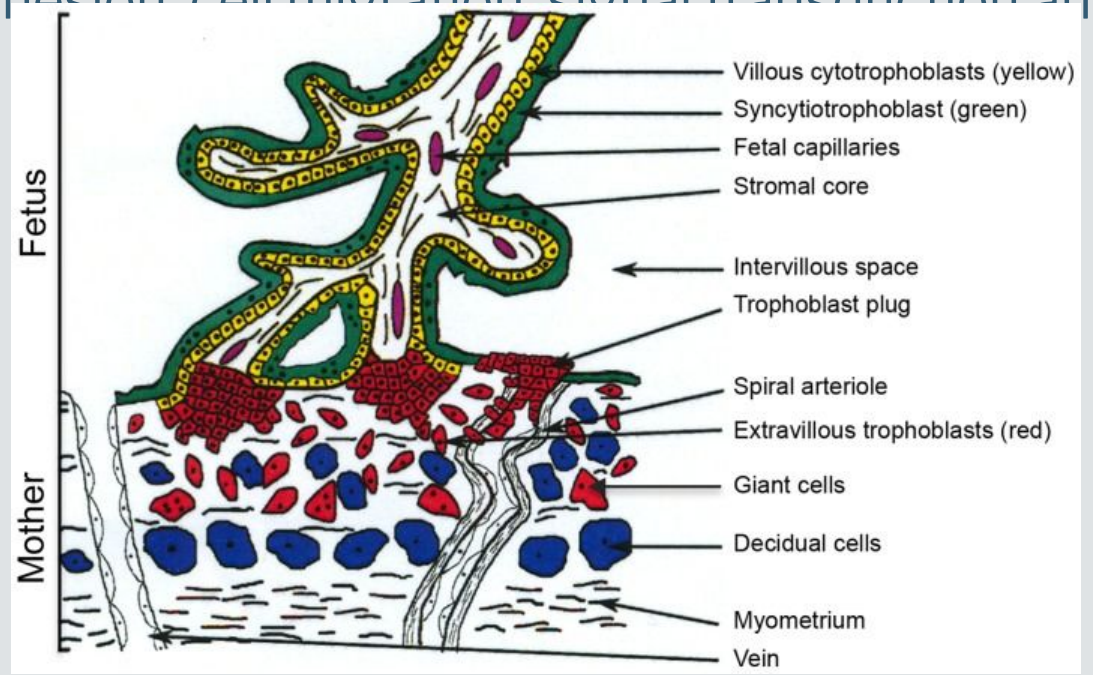
- Placenta accreta, and its most severe demonstration placenta percreta, invades through all the uterine layers and is considered a dangerous condition that may lead to a life threatening bleeding after the delivery.
- The most shared theory of placenta accreta pathogenesis is that defective decidualization involving the endometrial–myometrial interface, such as in areas of scarring caused by previous uterine surgery, allows the anchoring villi of the placenta to attach directly to or invade the myometrium.
- Prior cesarean delivery (CD) and placenta previa are independent risk factors for placenta accr





Introduction

- The two major cells in the placenta include villous trophoblasts (VT) and extravillous trophoblast (EVT). VT cells cover the chorionic villi and are involved in the exchange of gas and nutrients between the mother and the fetus, while EVT cells, which migrate and invade into the maternal endometrium, are one of the central components of human implantation and placentation.
- αvβ3 integrin is a heterodimeric transmembrane glycoprotein that facilitate cell–ECM adhesion, cell migration, signal transduction and cell to cell interaction.



Materials and methods

- Tissue and data collection
- IHC
- Protein extraction
- Western blotting
- Statistical analysis

Materials and methods

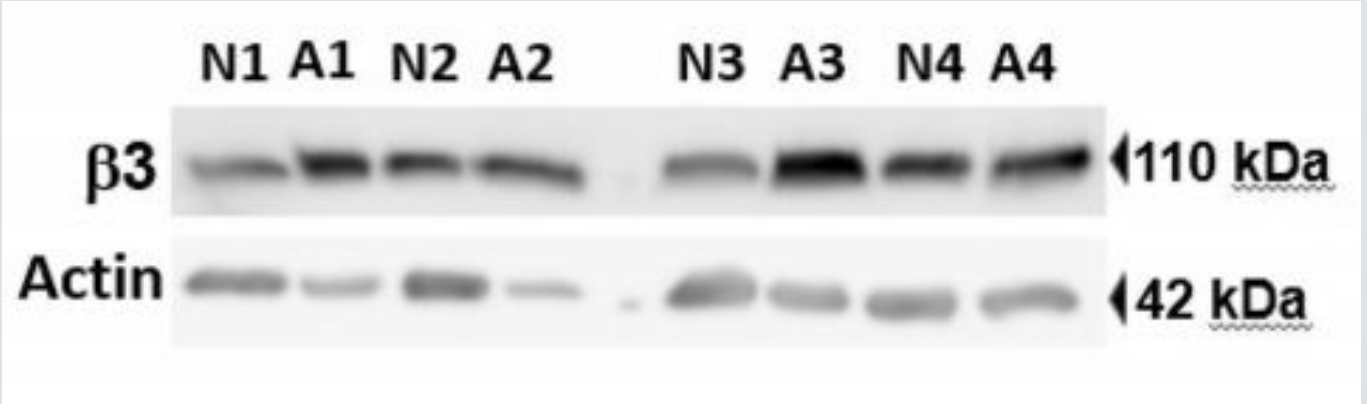
Characteristics	accreta ($N=10$)	Normal ($N=10$)	p value
Maternal age at screening (years)	32.75 ± 3.6	32.14 ± 4.36	0.54
Pre-pregnancy body mass index (kg/m^2)	21.64 ± 3.24	22.33 ± 4.29	0.51
Gravidity	3.1 ± 1.37	2.24 ± 1.43	0.37
Parity	1.9 ± 1.26	1.69 ± 0.99	0.78
Chronic hypertension (%)	2 (19%)	1 (9%)	0.39
Pregnancy complications (GDM, preclampsia) (%)	3 (28%)	1(9%)	0.14
Smoking (%)	3(28%)	1 (9%)	0.15
Gestational age at delivery	35.6 ± 3.36	37.5 ± 4.12	0.09
Cesarean section	10 (100%)	10 (100%)	

Data are presented as mean + SD or N (%)

- Baseline characteristics of the study group.

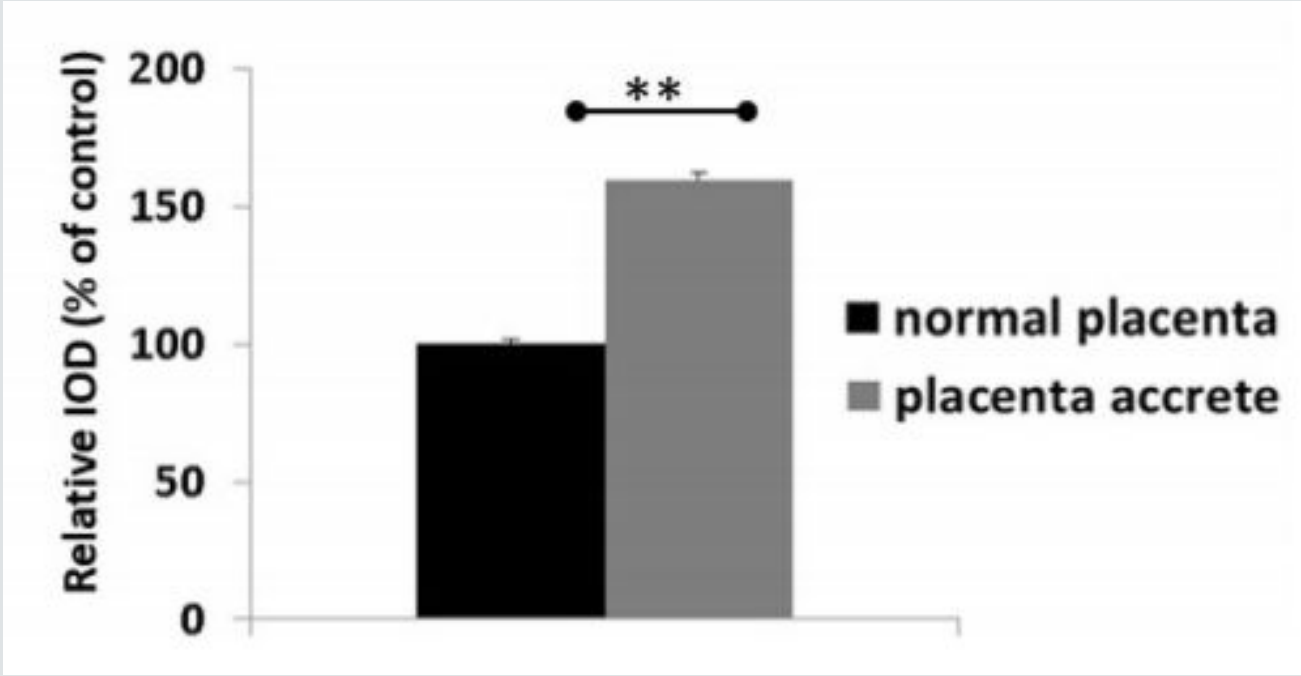
Results

- Total protein extraction from all placental tissues and following αvβ3 integrin expression assessment by WB using an anti β3 integrin monomer antibody showed significantly elevated αvβ3 protein levels in the percreta tissues compared to normal placentas ($p<0.05$).
- Representative WB results from four normal and four percreta placentas are depicted in the figure.
- Actin was used as a



Results

- Normalized quantification of the integrin level in the entire study cohort is shown in the figure.
- Significantly elevated αvβ3 protein levels in the percreta tissues compared to normal placentas ($p<0.05$).



Results

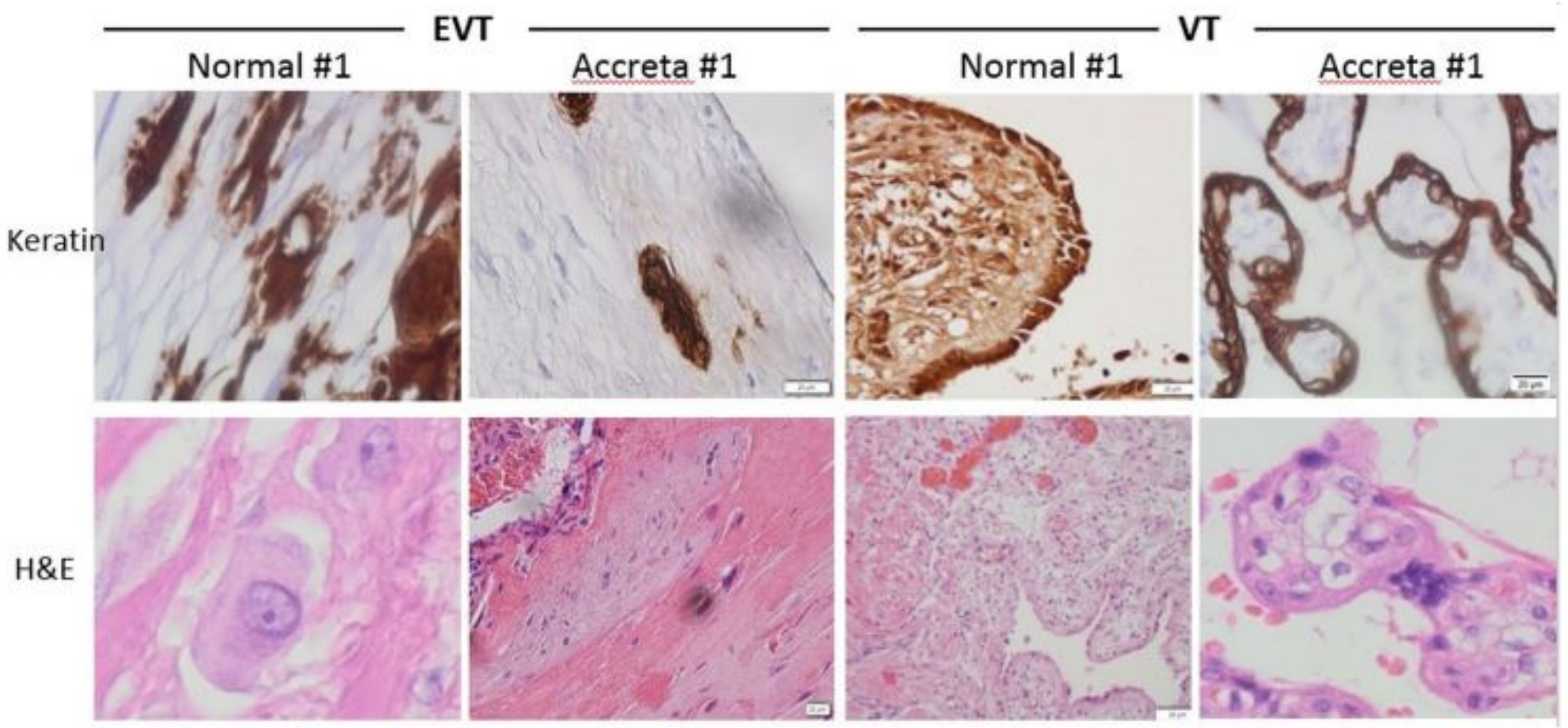
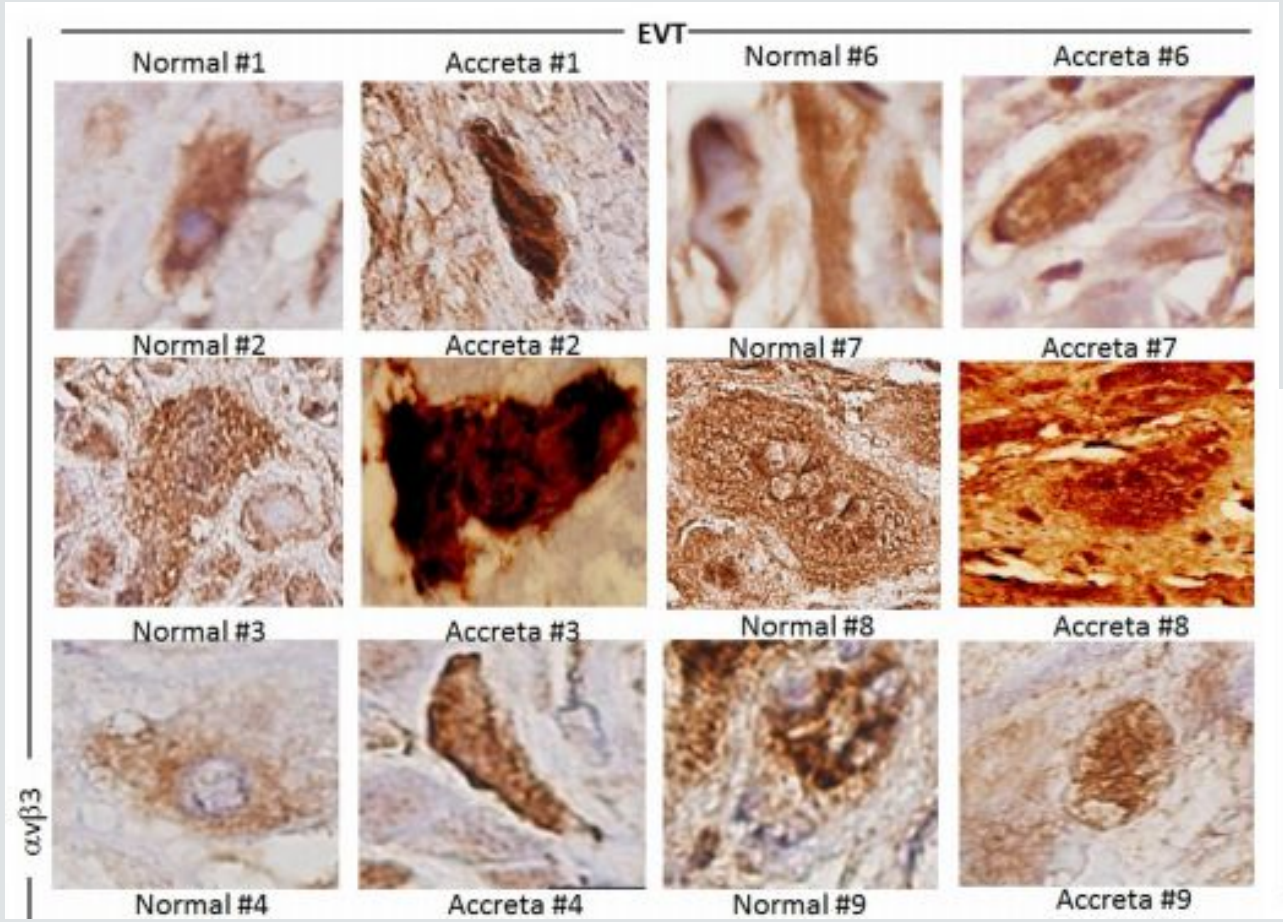
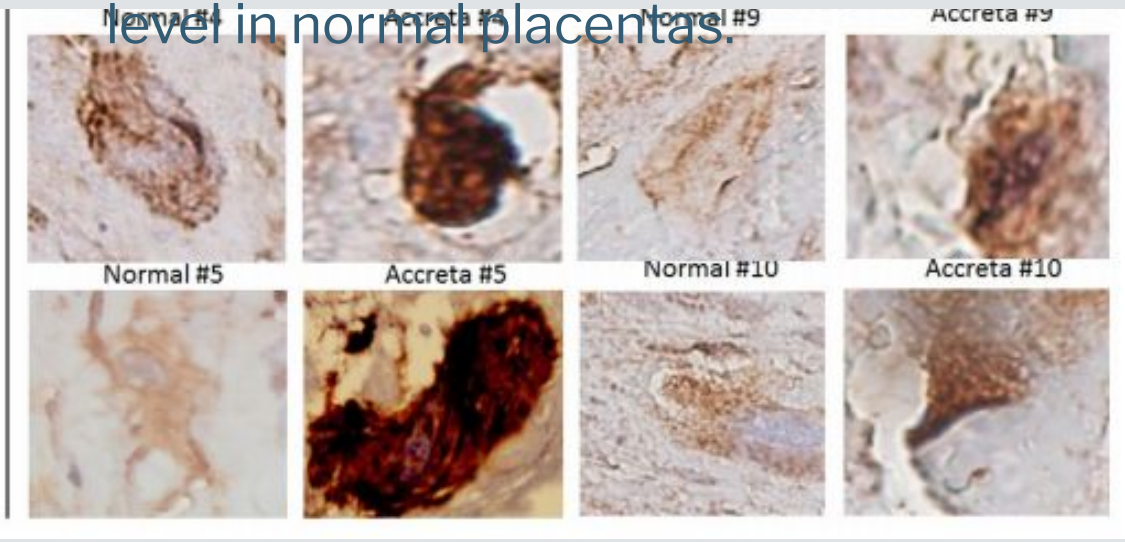


Fig. 2 Classical VT and EVT cells in representative samples from normal and accreta placentas. The various tissues were stained using H&E and anti-keratin 7 antibodies, a known trophoblast marker. Villous trophoblasts (VT) and extravillous trophoblasts (EVT). 40X magnification

Results

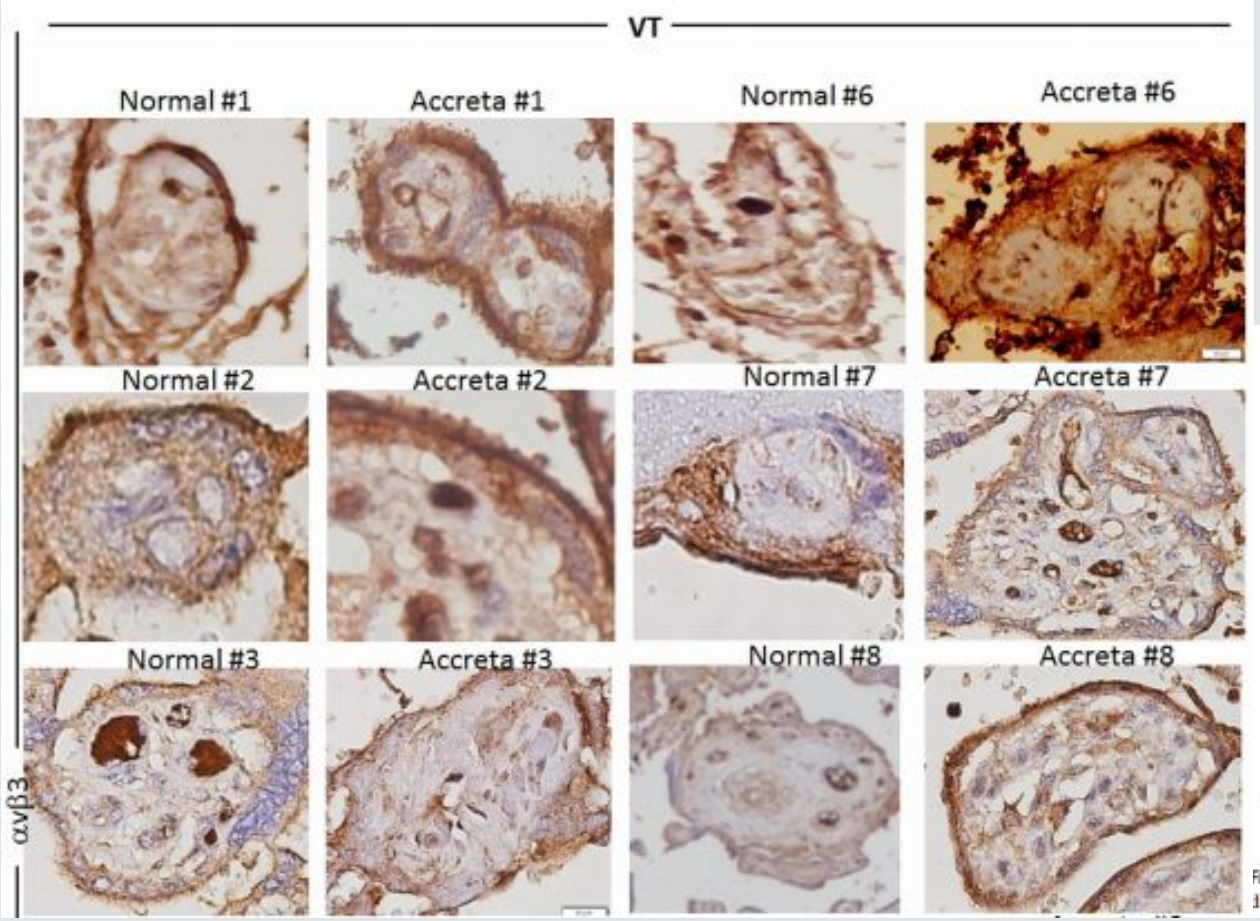


- Results of αvβ3 IHC staining in EVT cells in all collected placentas indicate that in the majority of percreta placentas (9 out of 10 tissues), EVT cells consistently exhibited signifcantly elevated αvβ3 integrin compared to the expression level in normal placentas.



- In the EVT cells the expression of αvβ3 was uniformly distributed.

Results



- In contrast, VT cells in the normal and percreta placentas demonstrates a comparable integrin expression (7 out of 10 tissues).

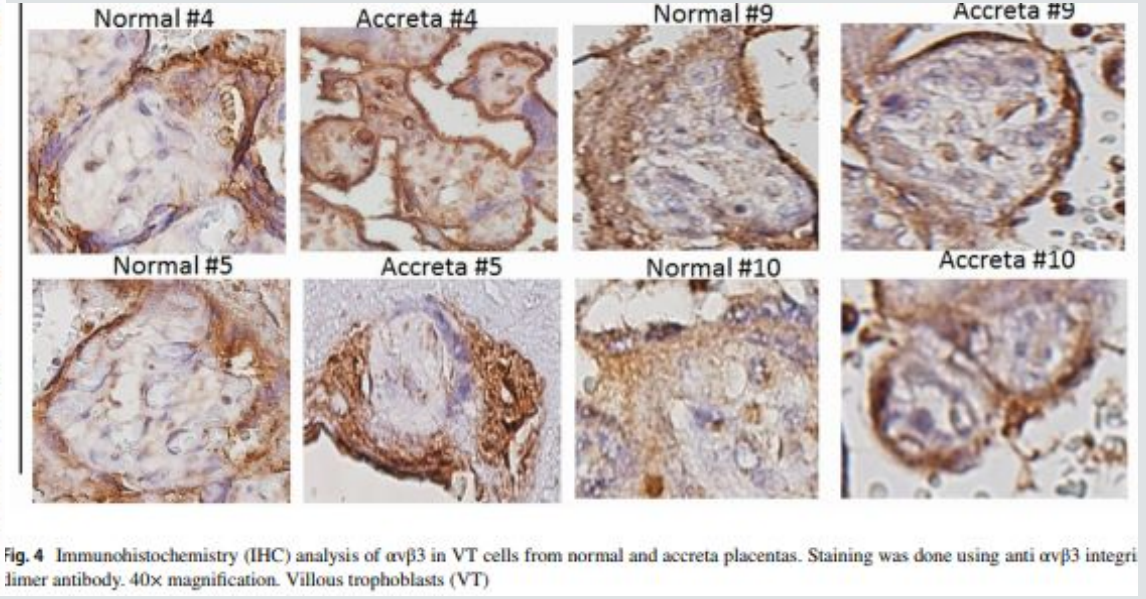
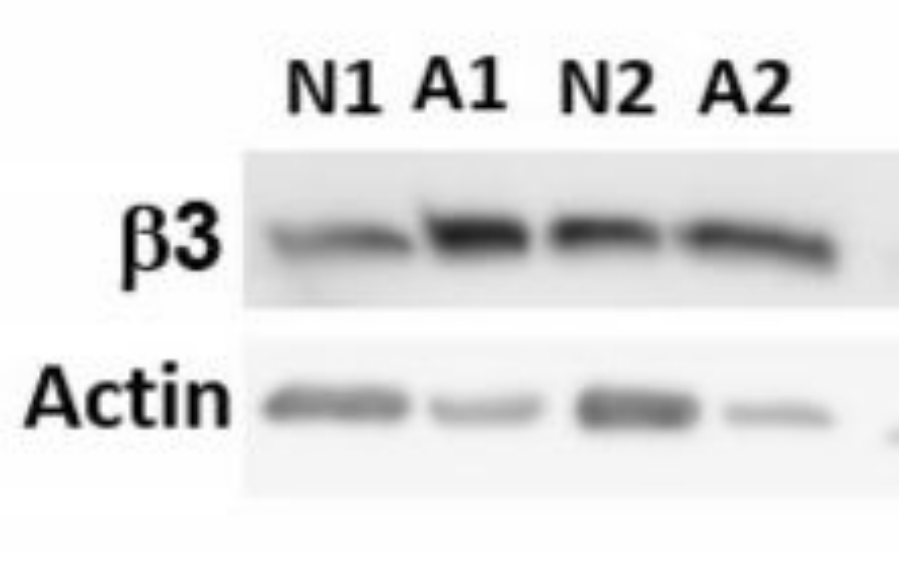


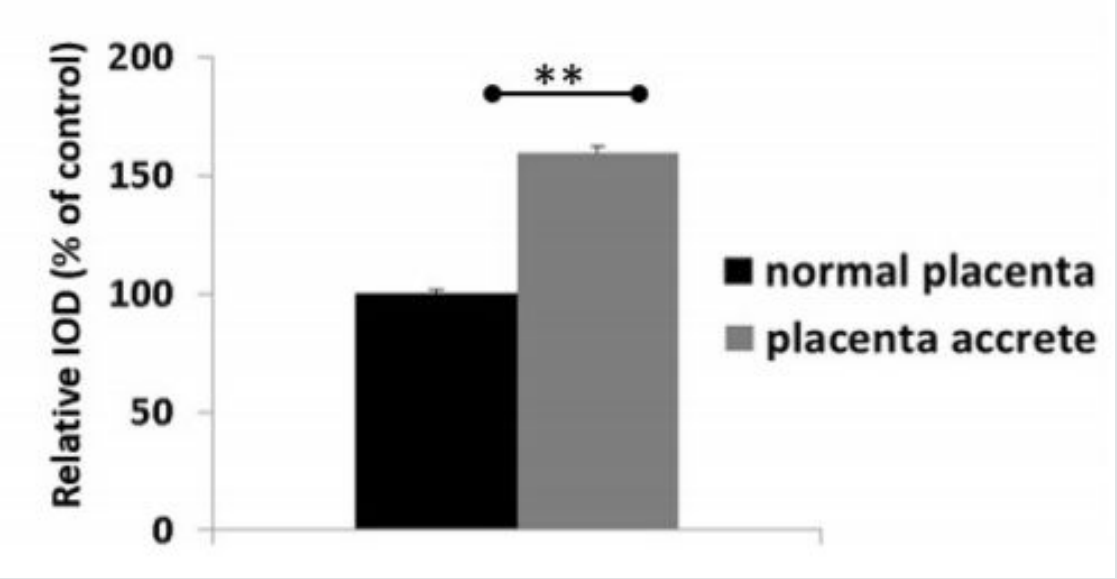
Fig. 4 Immunohistochemistry (IHC) analysis of αvβ3 in VT cells from normal and accreta placentas. Staining was done using anti αvβ3 integri limer antibody. 40× magnification. Villous trophoblasts (VT)

- In the VT cells the integrin was located mostly at the cell membrane, with an apical expression.

Discussion

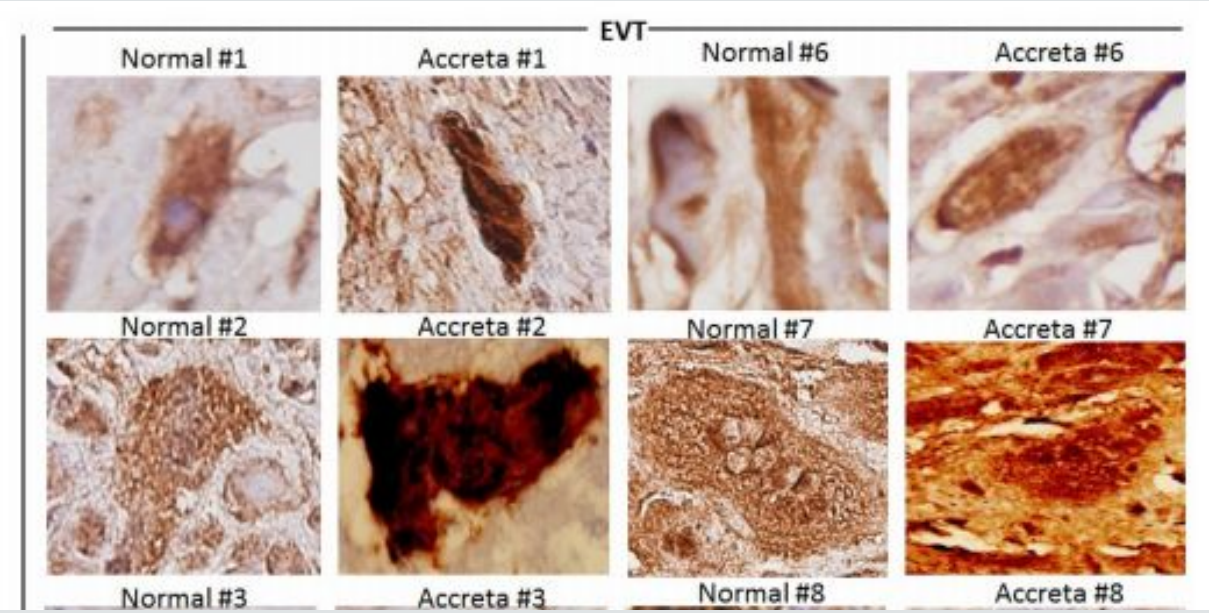
- We identified enhanced αvβ3 integrin expression in placenta percreta, compared to normal placentas, which mainly originated from EVT cells.
- We observed a membrane expression in VT cells and a uniformly diffused expression in EVT cells.
- We suggest that placenta percreta utilizes this specific integrin to display abnormal invasive phenotype.

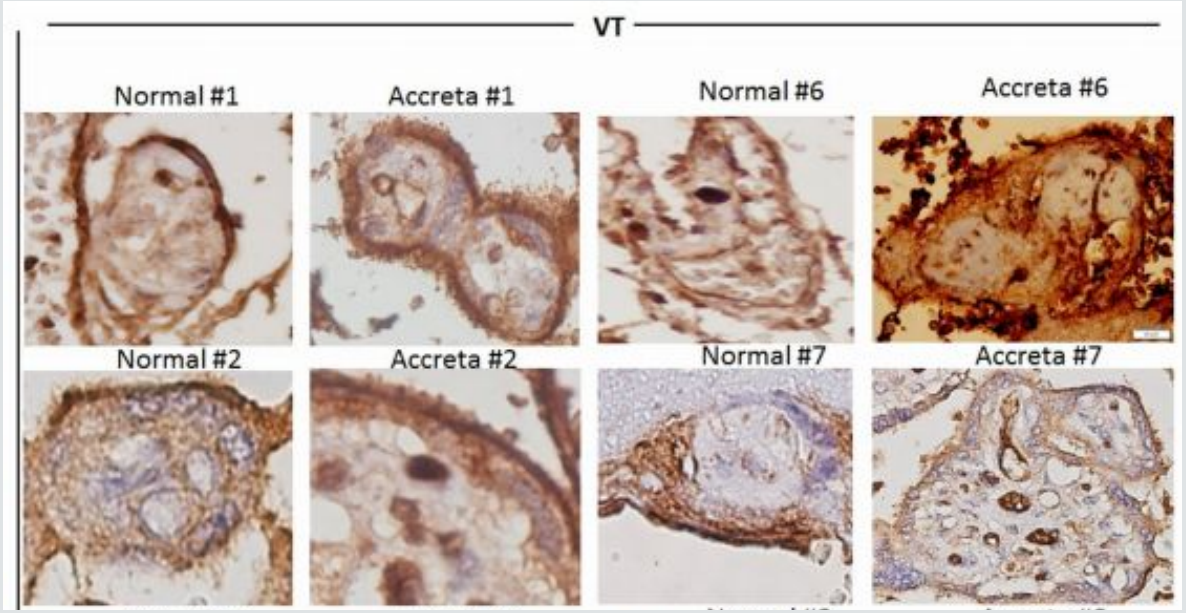




Discussion

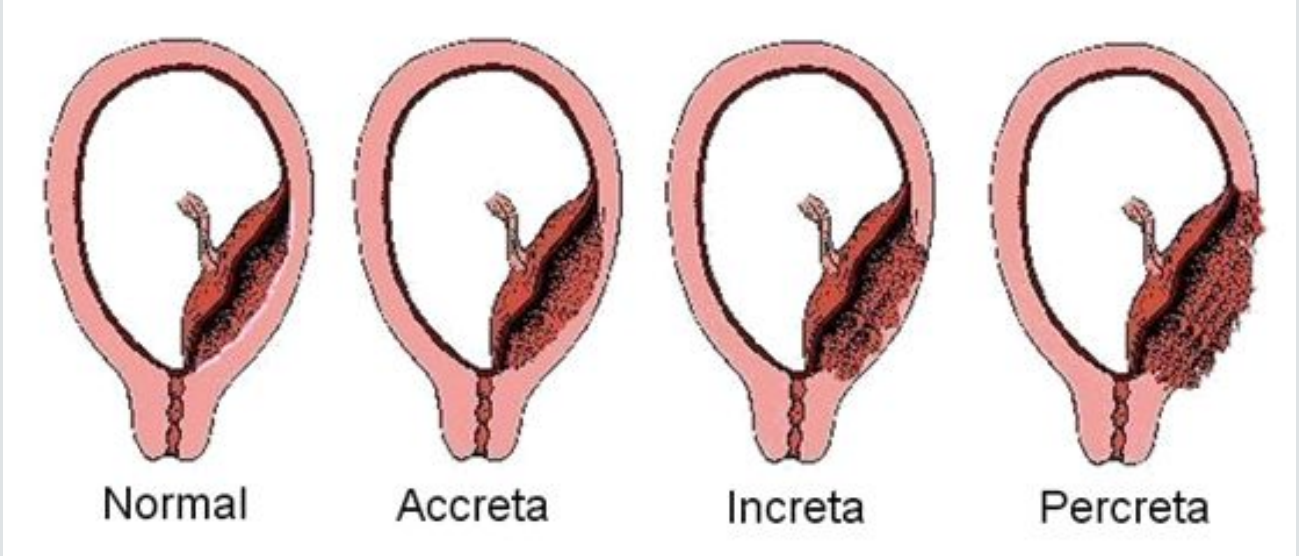
- To study the integrin localization we used an antibody that recognizes the full αvβ3 integrin dimeric form, and not the integrin monomers, as commonly used by others.
- Additional strength is provided by previous works on the integrin in EVT cells, which support their involvement in placenta accreta.
- Possible limitations are the small study size and its descriptive nature.





Conclusion

- αvβ3 integrin is overexpressed in placenta percreta tissues, originating mainly from EVT cells, and suggest for a potential function of this membrane receptor in the pathogenesis of this condition.
- Due to rarity of this condition, additional studies are needed to validate these findings in a larger study cohort. In addition, more work is merited in order to fully elucidate the biological role of αvβ3 integrin using in vitro and in vivo models.



Questions for discussion

1. What are the potential benefits of using knowledge of αvβ3 integrin overexpression in treatment and diagnosis of placenta accreta?
2. Does the discovery of αvβ3 integrin overexpression in EVT cells in placenta percreta significantly improves the understanding of the pathogenesis of placenta accreta?
3. What are the new perspectives and potential targets in studying the pathogenesis of placenta accreta?

Thank you for your attention!