differences were not observed amongst the groups upon treatment with isoflavone and an estrogen receptor antagonist, indicating that isoflavone acted via the estrogen receptor.
Conclusion: Isoflavone increases the mRNA expression levels of IL-6/gp130 in human endometrial glandular cells of early to mid secretary phase.

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P1.54.
THE SPIRALITY OF ARTERIES MAY BE IMPORTANT FOR NORMAL HUMAN PREGNANCY – A THEORETICAL PERSPECTIVE

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Development of the utero-placental interface during the first trimester of human pregnancy is mainly dependent on the activity of cytotrophoblast cells which invade the maternal decidualised endometrium to anchor the conceptus in place. Cytotrophoblast also remodel the spiral arteries, replacing the endothelial and smooth muscle layers with endovascular cytotrophoblast and fibrinoid. This process generates strong connections between the villi and cotyledons, the cytotrophoblast shell, and the uterine spiral arteries, and shows that these connections are formed during the first trimester of pregnancy.
The radius of the placenta at the end of the first trimester is approximately 2.5cm, and it continues to increase in size during the remainder of pregnancy; the term placenta has a radius of about 10cm. The aim of this abstract is to consider what this increase in placental size might imply for the anatomy of the utero-placental interface.
As the placenta grows laterally during the last 6 months of pregnancy, the strong connections to the decidua mean that the uterus will be stretched over this area of interface with placenta; the non-pregnant uterus is no more than 10cm in any direction, so it must be stretched by the term (20cm) placenta. This lateral growth may impose strains on the spiral arteries, which are connected to the maternal vascular supply at one end, and to the placenta at their terminus. However, the spirality of the arteries means that the terminal (placental) end could move further laterally than the connection to the main uterine vessels, and retain the physical connections at both ends of the spiral arteries. The arteries would become less spiral during this process of stretching – and decreased spirality has been observed in other studies. This suggests that the spirality of 'spiral arteries' may be necessary for normal human pregnancy.

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P1.55.
POST TRAUMATIC STRESS DISORDER (PTSD): THE HIDDEN MORBIDITY OF ABNORMALLY INVASIVE PLACENTA (AIP)

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Objectives: Emergency postpartum hysterectomy (EPH) and significant postpartum haemorrhage (PPH) have been shown to be associated with an increased risk of PTSD. Planned AIP deliveries usually include hysterectomy and are frequently complicated by severe bleeding. It has, however been assumed that as women with an antenatal diagnosis of AIP are prepared for these adverse outcomes, they are less likely to develop PTSD than women with unexpected PPH/EPH. This study aims to investigate if women with AIP are more likely to screen positive for PTSD than those who had an uncomplicated caesarean delivery (CD) and how this compares to women who experienced unanticipated EPH/PPH.
Methods: A postal questionnaire containing a validated screening tool for PTSD was sent to four cohorts: women referred to a specialist clinic who were antenatally diagnosed with AIP, which was confirmed at delivery; women who had an uncomplicated CD; women referred to a specialist clinic who were not diagnosed with AIP and subsequently had an uncomplicated CD; and women who had had unexpected EPH and/or severe (>3000mls) PPH.
Results: Responses revealed significantly higher PTSD screening scores for AIP (p=0.001) and EPH/PPH (p=0.005) patients compared to both control groups (Fig. 1). No significant difference in scores was seen between AIP and EPH/PPH (p=0.211).
Conclusions: Fifty percent of women with antenatally diagnosed AIP screened positive for severe PTSD as a result of their delivery experience. This is comparable to those who had an unexpectedly traumatic delivery. This is the first study of its kind, and it reveals a significant, hidden morbidity associated with AIP diagnosis. These results should inform future postnatal management of AIP. We propose the initiation of a postnatal PTSD screening and intervention program for AIP patients, establishment of peer support groups and better education for families and primary healthcare professionals.

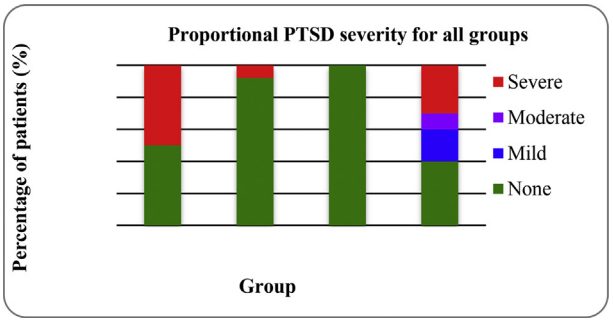

Fig. 1. Proportional PTSD severity for all groups.

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P1.56.
IN VITRO MODELS FOR STUDYING ENDOMETRIAL RECEPTIVITY - CHARACTERIZATION OF HUMAN BIOPSIES IN A NEW TEST SYSTEM

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Objectives: A basic requirement for human embryo invasion which comprises penetration of endometrial epithelial cells (EECs) by trophoblast cells is the appropriate preparation of the endometrium. Cyclic differentiation of endometrial cells, which is controlled by ovarian steroid hormones, leads to a short receptive period called window of implantation (WOI). As we could show previously, the WOI is characterized among other histological and biochemical changes by an altered distribution of adhering junctions in EECs which indicates a change in EEC polarity during the WOI.
Methods: To elucidate basic mechanisms of early human implantation we established a new 3D cell culture confrontation system. In this cell culture system we studied trophoblast-endometrial interaction by confronting gland-like spheroids of different endometrial adenocarcinoma cell lines with trophoblast cells. We further focused on the study of primary endometrial cells from scratch biopsies of women undergoing assisted reproductive technology (ART).
Results: Using confocal microscopy we could show that EEC cell line spheroids with a junction distribution similar to EECs during the WOI in vivo were more strongly invaded by the extravillous trophoblast cell line AC-1M88 than highly polarized EEC cell lines. First results on primary EEC cultures could be obtained showing close trophoblast-endometrial interactions. By use of light sheet microscopy we achieved a particularly high resolution of the invasive processes in real-time. Further studies are in progress to analyze the influence of 17beta-estradiol and progesterone on EEC receptivity and the invasiveness of trophoblast cells in the 3D confrontation culture system.
Conclusion: By applying a newly established 3D trophoblast invasion assay on tissue samples from patients undergoing ART, we expect new

insights into basic mechanisms of human implantation. Data obtained from this new confrontation approach may help to find new therapeutic strategies in ART treatment.

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P1.57.
ISOLATION OF A PERMANENT BOVINE ENDOMETRIAL GLAND CELL LINE (BEGC) WHICH RETAIN THEIR EPITHELIAL PHENOTYPE IN VITRO

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Background: Uterine glands (UG) play a major role for the histotrophic nourishment of the mammalian embryo during early pregnancy. Uterine gland knockout models have shown that UG are essential for embryo survival/development. Embryonic mortality occurs within the first two weeks of early pregnancy and is major problem in animal and human obstetrics. We hypothesize that impaired UG-trophoblast interaction is a leading cause of embryonic death during cattle implantation.
Aim: Isolate and characterize a permanent endometrial gland cell line from cattle.
Methods: The bovine endometrial gland cell (BEGC) line was isolated from endometrium. BEGC was characterized according to its morphology (light & electron microscopy), epithelial marker expression (immunofluorescence-IF) and trans-epithelial-resistance (TEER). The expression of components of the interferon tau system (IFNτ) and steroid receptors was analyzed by RT-PCR. BEGC was seeded in in three-dimensional gels to form acini which were characterized by light and electron microscopy and immunohistochemistry (IHC).
Results: BEGC displayed an epitheloid phenotype and ultastructural characteristic like apical microvilli (TEM/SEM). By use of IF the expression of epithelial markers (e.g. ezrin) could be confirmed. When seeded on inserts BEGC established TEER values over 2000 Ω/cm^2. Presence of mRNA transcripts of the IFNτ system (IFNAR1/2) and the estrogen (E_2) and progesterone (P_4) system (ESR1/2, PR isoform A/B, PGRMC1/2) was also confirmed. In gels BEGC formed acini consisting of polarized, keratin and ezrin positive cells. Additionally BEGC generated entire ductal systems (TEM/SEM).
Conclusion: We have established a permanent endometrial gland cell line from cattle (BEGC). The cells retain their epithelial phenotype during culture and express main components of the IFNτ and E_2/P_4 system. The self-aggregation of gland cells (acini in vitro) ultimately proves the isolated cell line to be gland cells. In the future BEGC will serve as an in vitro model to further understand cell-cell interactions during implantation in cattle.

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P1.58.
ROLE OF VIP IN TROPHOBLAST INVASION, VASCULAR REMODELING AND IMMUNOMODULATION DURING EARLY PREGNANCY

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Deep placentation disorders are associated with impaired invasiveness of extravillous trophoblast cells (EVT) and vascular remodelling in a pro-inflammatory microenvironment. The vasoactive intestinal peptide (VIP) has anti-inflammatory, pro-secretory and vasodilating effects. However its role in pregnancy is still unclear.
Objectives: Here we studied the expression and effects of VIP in human first trimester placenta and its modulation on decidual macrophages (dMA) and NK cells (dNK).
Methods: Explants from placentas (5-10 weeks) were treated with VIP ±VIP-neutralizing antibody (α-VIP) and outgrowth was measured. VIP expression and spiral artery (spA) remodelling were studied by immunostaining assays. Positive selection with CD14 or CD56 immunomagnetic beads was used to isolate dMA and dNK. Both cells were treated with VIP. Gene expression and protein secretion was studied by qRT-PCR and Bio-Plex assay, respectively.
Results: Explants treated with VIP increased the outgrowth of EVT (592±68.6 A.U.) and the effect was prevented by α-VIP (266±100.1 A.U.). VIP was expressed in the cell columns, the villous and EVT cells. Moreover, HLA-G/VIP positive cells were found in both the walls and lumens of spA being remodelled. The BioPlex assay showed high levels of IL-1β and IL-6 and low concentration of pro-inflammatory cytokines (TNF-α, IL-12). When the explants were treated with VIP, the anti-inflammatory cytokine IL-10 and chemokines IL-8, RANTES, IP-10 and MCP-1 were increased with no changes in pro-inflammatory cytokines.
VIP increased IL-10 and reduced IL-2 and IL-12 in dMA whereas it reduced IL-1β and IL-8 in dNK. VIP also increased metalloprotease-2 in dMA but not in dNK.
Conclusion: The results suggest that VIP is produced by trophoblast cells and support its role in migration, invasion and spA remodelling by EVT. Moreover, VIP regulates the immune microenvironment through inducing chemokine expression and increasing IL-10 production without changing pro-inflammatory cytokines.

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P1.59.
POSSIBLE ROLES OF UTERINE PGRMC1 IN THE IMPLANTATION AND DECIDUALIZATION

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Objective: Progesterone (P4) receptor membrane component 1 (PGRMC1) is a P4 binding protein that could mediate P4's action via non-canonical P4 signaling pathway. Although the conditional ablation of uterine PGRMC1 results in subfertility in mice, the precise role of PGRMC1 in the uterus remains unknown. In this study, we examined the expression of PGRMC1 in rat uterus during the peri-implantation period and the effect of PGRMC1 inhibitor on the expression of implantation- and decidualization-associated factors in human endometrial cells.
Methods: Wistar-Imamichi strain rats were mated, and pregnant uteri were collected from day 3 to day 9 of pregnancy. A delayed implantation model and an artificially induced decidualization model were also used to determine the correlation between PGRMC1 expression and these processes. The expression of PGRMC1 protein in uteri was evaluated by immunohistochemical analysis. Human endometrial stromal cells (ESC) and glandular epithelial cell line (EM1) were pre-treated with AG-205, a PGRMC1 inhibitor and then stimulated with dibutyryl-cAMP (db-cAMP) for 48 hours. The mRNA levels of implantation-related enzyme, cyclooxygenase 2 (COX2), and decidual markers, insulin-like growth factor binding protein-1 (IGFBP-1) and prolactin (PRL) were investigated by quantitative RT-PCR.
Results: PGRMC1 was predominantly expressed in glandular and luminal epithelial cells in days 3 and 5 of pregnant uterus. On days 7 and 9 of pregnancy, PGRMC1 was detected in decidua surrounding attached embryo and mesometrial stroma at the implantation sites. Furthermore, enhanced PGRMC1 expression was observed in the decidua in artificially induced decidualization model. Of note, treatment of EM1 and ESC with AG-205 significantly upregulated db-cAMP-induced COX2 expression. The db-cAMP-stimulated IGFBP-1 and PRL expression was also increased by AG205 in ESC.
Conclusion: These findings suggest possible roles of uterine PGRMC1 in implantation and decidualization during early pregnancy.

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