



IFPA meeting 2018 workshop report II: Abnormally invasive placenta; inflammation and infection; preeclampsia; gestational trophoblastic disease and drug delivery



Christiane Albrecht^a, Larry Chamley^b, D. Stephen Charnock-Jones^c, Sally Collins^d, Hiroshi Fujiwara^e, Thaddeus Golos^f, Solene Grayo^g, Natalie Hannan^h, Lynda Harrisⁱ, Kiyotake Ichizuka^j, Nicholas P. Illsley^k, Mitsutoshi Iwashita^l, Sampada Kallol^a, Abdulla Al-Khan^k, Gendie Lash^m, Takeshi Nagamatsuⁿ, Akitoshi Nakashima^o, Kaoru Niimi^p, Masataka Nomoto^p, Christopher Redman^d, Shigeru Saito^o, Kenji Tanimura^q, Masatoshi Tomi^r, Hirokazu Usui^s, Manu Vatish^d, Bryce Wolfe^f, Eiko Yamamoto^p, Perrie O'Tierney-Ginn^{t,*}

^a University of Bern, Switzerland

^b University of Auckland, New Zealand

^c University of Cambridge, UK

^d University of Oxford, UK

^e Kanazawa University, Japan

^f University of Wisconsin-Madison, USA

^g Institut Pasteur of Shanghai, China

^h University of Melbourne, Australia

ⁱ University of Manchester, UK

^j Showa University, Northern Yokohama Hospital, Japan

^k Hackensack University Medical Center, USA

^l Kyorin University, Japan

^m Guangzhou Women and Children's Medical Center, China

ⁿ The University of Tokyo, Japan

^o University of Toyama, Japan

^p Nagoya University, Japan

^q Kobe University, Japan

^r Keio University, Japan

^s Chiba University, Japan

^t Mother Infant Research Institute, Tufts Medical Center, Boston, MA, USA

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ABSTRACT

Workshops are an important part of the IFPA annual meeting as they allow for discussion of specialized topics. At IFPA meeting 2018 there were nine themed workshops, five of which are summarised in this report. These workshops discussed new perspectives and knowledge in the following areas of research: 1) preeclampsia; 2) abnormally invasive placenta; 3) placental infection; 4) gestational trophoblastic disease; 4) drug delivery to treat placental dysfunction.

1. Preeclampsia and the placenta: what's new?

Chairs: Christopher Redman and Mitsutoshi Iwashita.

Speakers: Larry Chamley, Stephen Charnock-Jones, Akitoshi Nakashima, Manu Vatish.

1.1. Outline

Preeclampsia is caused by the presence of the placenta although maternal factors are critical for development of the maternal syndrome. In this workshop four speakers described new developments which

* Corresponding author. Mother Infant Research Institute Tufts Medical Center, 800 Washington St, Box #394, Boston, MA, 02111, USA.

E-mail address: potierneyginn@tuftsmedicalcenter.org (P. O'Tierney-Ginn).

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enlarge the bigger picture of this complex disorder.

1.2. Summary

Larry Chamley reminded us that, of the maternal factors that induce pre-eclampsia, antiphospholipid autoantibodies are one of the most powerful, increasing a woman's risk nearly tenfold. He summarised how they adversely affect syncytiotrophoblast to contribute to the pathology of the disease. The autoantibodies are transported from maternal blood into the syncytiotrophoblast where they interact with mitochondria and activate the cell death machinery. Rather than inducing cell death, antiphospholipid antibodies induce endoplasmic reticulum stress and the production of extracellular vesicles (EVs) that contain increased amounts of “danger signals”, including mitochondrial DNA. These dangerous EVs cause the activation of maternal endothelial cells - a hallmark of preeclampsia.

Akitoshi Nakashima described the importance of placenta-specific autophagy in his mouse model of pre-eclampsia. If this autophagy is inhibited it elicits failure of invasion and vascular remodeling, resulting in poor placentation. Then chronic hypoxia of these poorly structured placentas induces downregulation of transcription factor EB (TFEB), a master regulator of autophagy, in trophoblasts. Increased aggregation of protein ensues, associated with the impaired placentation. Observations in human tissue were consistent with this model.

Stephen Charnock-Jones and his colleagues set out to investigate why the risk of perinatal and infant death is greater in male fetuses exposed to placental dysfunction. They applied several “-omic” technologies to placenta and maternal serum of affected and unaffected pregnancies. They searched for differences in placental function associated with fetal sex, using data and biological samples from the Cambridge Pregnancy Outcome Prediction (POP) study. They found that spermine synthase (*SMS*) mRNA and protein are more abundant in the female than in the male placenta. *SMS* is an X-chromosome gene and its promoter methylation profile is similar to other genes that escape X-inactivation (XCI). However the escape is restricted to the placenta. *SMS* was reduced in male primary trophoblast cells, which were more sensitive to polyamine depletion. The spermine metabolite N1,N12-diacetylspermine (DiAcSpm) was found to be higher in the female placenta and sera of women carrying a female fetus. They made the surprising observation that higher DiAcSpm in maternal serum increased the risk of preeclampsia but reduced the risk of fetal growth restriction (FGR). This intriguing finding is the first to identify a maternal biomarker with opposite associations with preeclampsia and FGR. It is also the first evidence that implicates polyamine metabolism in sex-related differences in human pregnancy complications.

Manu Vatish described -omic investigations of syncytiotrophoblast extracellular vesicles that circulate in maternal blood. They were prepared by dual lobe placental perfusion. This is the most physiological *ex vivo* technique for isolating extracellular vesicles to enable separation into microvesicles and exosomes. Samples from normal and pre-eclampsia placentae were subjected to comprehensive proteomics and deep sequencing analysis. Their bioinformatics analysis showed that there are specific differences between microvesicles and exosomes, in the diseased and normal state. Vatish and colleagues validated these changes and reveal a number of novel and promising biomarkers of pre-eclampsia that can be measured in the maternal circulation. This strengthens the concept that pre-eclampsia is secondary specifically to syncytiotrophoblast factors that are shed into the maternal circulation.

1.3. Conclusions

All four speakers presented novel methods and results from very different points of view. They included (1) the role of trophoblast autophagy of syncytiotrophoblast in early pregnancy; (2) the effect of syncytiotrophoblast damage secondary to antiphospholipid autoantibodies that generates release of syncytiotrophoblast extracellular

microvesicles bearing danger molecules; (3) sex specific differences in polyamine metabolism in placentas; and differences in circulating polyamine metabolites that have opposite associations with pre-eclampsia and fetal growth restriction; (4) the application of dual lobe placental perfusion and -omics techniques to demonstrate the range and heterogeneity of potential signals released from syncytiotrophoblast; new potential disease biomarkers were discovered in this way for further testing and validation.

2. Abnormally invasive placenta (AIP): an international perspective

Chairs: Sally Collins and Kiyotake Ichizuka.

Speakers: Sally Collins, Nicholas Illsley, Abdulla Al Khan, Kenji Tanimura.

2.1. Outline

The aim of the workshop was to present and discuss recent advances in diagnosis and management of abnormally invasive placenta. The workshop was fully interactive with questions posed by both the speakers and the audience. These were answered via smartphone with the results displayed real time throughout.

2.2. Summary

Sally Collins introduced the International Society for AIP (<http://www.is-aip.org>). The IS-AIP evolved from the European Working Group on AIP (EW-AIP) and currently consists of 42 Obstetricians, Gynecologists, Pathologists, Anesthesiologists and Basic-Science Researchers from 13 European countries. The aim of the group is to promote excellence in all aspects of healthcare relating to AIP including research (clinical, epidemiological and ‘wet lab’), diagnosis/management, and education. It has published ultrasound markers for AIP (Collins et al., *Ultrasound Obstet Gynecol*, 47(3): 271-5, 2016) and is in the process of producing an evidence-based guide for intrapartum management. The IS-AIP welcomes new members from around the world.

Kenji Tanimura discussed prenatal diagnosis of AIP in women with placenta previa. Abnormally invasive placenta is a life-threatening obstetrical condition, and placenta previa (PP) is one of the most significant risk factors for AIP. Prenatal diagnosis of AIP helps to minimize clinical complications by enabling obstetricians to plan for resources required during delivery. At Kobe University, pregnant women with PP who are suspected of having AIP receive preoperative internal iliac artery occlusion balloon catheter placement for reducing intraoperative blood loss. Their novel Placenta Previa with Adherent Placenta (PPAP) scoring system for predicting AIP in women with PP was also introduced. The PPAP score is composed of 1) past history of previous uterine surgery; and 2) imaging findings of ultrasonography and MRI (Tanimura et al., *Placenta* 64, 27-33, 2018). Tanimura and colleagues have found that PPAP score may be useful for predicting AIP complicated by PP.

Through video recordings, **Abdulla Al Khan** demonstrated surgical techniques and methods used to manage abnormally invasive placentation at delivery. Hemorrhage is the leading cause of maternal morbidity and mortality in the setting of women with AIP. The objective of the presentation was to provide surgeons involved in the care of these complex patients a systematic surgical approach in order to decrease morbidity.

Current knowledge regarding the pathology of AIP was presented by **Nicholas Illsley**. Many women who have both placenta previa and uterine damage (e.g. Cesarean section) – primary risk factors for AIP- do not progress to AIP. Thus, other factors, perhaps cellular or molecular, may be involved. Illsley and colleagues examined the status of trophoblast cells on the epithelial-mesenchymal transition spectrum and

showed that while cytotrophoblasts were converted to a metastable, mesenchymal form of extravillous trophoblast (EVT) in the first trimester, third trimester EVT regressed to a less invasive, more epithelial phenotype. EVT isolated from AIP pregnancies were found to be intermediate between the first and third trimester EVT, implying a more invasive, mesenchymal endpoint than normal third trimester EVT, consistent with an over-invasive phenotype. They postulated that an abnormal or deficient decidua/myometrium is responsible for the impaired regression seen in AIP. Future directions involve identifying endometrial factors predisposing to AIP with the intent of therapeutic modification to reduce the risk of AIP.

2.3. Conclusions

A lively debate ensued regarding all of the issues covered. With regards to imaging, the opinion was that no single sign has been demonstrated to be diagnostic. Novel scoring systems, such as the one presented, may assist with this. A discussion regarding the possible option of conservative management followed the talk on surgical techniques. Although there was disagreement on the utility of this strategy, all were in agreement that the management offered should be an individualized decision taken on a case by case basis. Novel strategies for investigating AIP at a cellular level were also extensively discussed.

3. Impact of infection on placental biology

Chairs: Gendie Lash and Shigeru Saito.

Speakers: Thaddeus Golos, Solene Grayo, Gendie Lash, Shigeru Saito, Kenji Tanimura, Bryce Wolfe.

3.1. Outline

The establishment of a successful pregnancy involves invasion of the maternal uterine tissues by fetal extravillous trophoblast cells (EVT) and remodeling of the uterine spiral arteries. Both of these processes are tightly regulated by a range of cell types, most notably the uterine natural killer cells (uNK) and uterine macrophages, which play important ‘non-immune’ roles in establishment of pregnancy. But what happens when the pregnancy is compromised by an infectious agent? Do the immune cells become repurposed so that they are no longer able to perform their tissue remodeling roles? Does the immunosuppressed environment of the fetal-maternal interface allow for a greater degree of viral/bacterial infection? Upon infection is placental function compromised? This workshop explored some of these questions using emerging knowledge from studies on viral (Zika, CMV) and bacterial (*Listeria*) infection during pregnancy.

3.2. Summary

Gendie Lash reviewed non-immune roles of decidual immune cells in early pregnancy. In early pregnancy 30% of the decidual stromal cells are leucocytes, predominantly uterine natural killer (uNK) cells (70%), macrophages (25%) and T cells (5%). These different cell types play essential roles not only in establishment of tolerance to the semi-allogeneic fetus but also in regulation of EVT invasion and, in particular, remodeling of the uterine spiral arteries. Evidence for the different roles uNK cells and macrophages play was presented and several discussion points raised. In particular, why does spiral artery remodeling fail in some pregnancies, and are bacterial or viral infections a cause of this by altering the phenotype of decidual immune cells so that they can no longer perform their non-immune functions?

Solene Grayo posed the question: what can we learn from each congenital pathogen that can be applied to others? During pregnancy, the syncytiotrophoblast is an efficient physical and chemical antimicrobial barrier. Thus, most pathogens affecting the mother do not

cause congenital fetal infection. Nevertheless, a few predominantly intracellular microbes (e.g. *Listeria monocytogenes*) are able to bypass these intrinsic defenses and invade the syncytium by using specific virulence determinants, such as internalins for *L. monocytogenes* (internalin-mediated invasion). Moreover, directly in contact with maternal cells in the uterus, EVT represent a possible pathway into the placenta and are targeted by microbes to facilitate vertical transmission (*Toxoplasma gondii*, *L. monocytogenes*, HCMV). The invasion of maternal immune cells, prior to EVT invasion of the uterus, is also described. Microorganisms (viruses, parasites and bacteria) use various ways to breach the placental barrier. Nevertheless, evidence that multiple congenital pathogens share common strategies is emerging, allowing to better predict the potential of new “TORCH” pathogens, such as Zika virus (ZIKV).

Kenji Tanimura discussed pathological mechanisms of placental cytomegalovirus (CMV) infection, and their identification of biomarkers for predicting congenital CMV infection. Human CMV is one of the most common causes of mother-to-child infection worldwide. Congenital CMV infection can lead to neonatal death and major neurological sequelae in surviving infants. Recent studies demonstrate that not only direct effects of CMV on the fetus but also indirect effects of CMV by placental infection may cause adverse pregnancy outcomes. The detection of CMV-DNA in maternal uterine cervical secretions is a predictive biomarker for congenital infection in high-risk pregnant women, whereas maternal universal screening based on CMV IgG, IgM or IgG avidity index overlooks a number of newborns with congenital-infection in low-risk pregnant women. He also reported that threatened premature delivery was associated with the occurrence of congenital infection from non-primary infection.

Thaddeus Golos reported that although frank birth defects are uncommon with experimental infection of pregnant nonhuman primates (NHP) with Zika virus (ZIKV), early pregnancy infection is associated with a significant increase in adverse pregnancy outcomes, including miscarriage, preterm labor, stillbirth, and postnatal respiratory distress. These adverse outcomes are associated with placental and decidual vascular pathology and placental infarcts. Altered placental and decidual macrophage phenotypes and prevalence have been noted with infection. The reported tropism of ZIKV for Hofbauer cells suggests that this may be one pathway by which ZIKV causes placental insufficiency associated with adverse outcomes.

Bryce Wolfe presented their work in collaboration with Dr Leticia Reyes on oral pathogens and placental dysfunction. *Porphyromonas gingivalis* (Pg) is a periodontal pathogen implicated in pregnancy complications involving defective placentation. Pg strains that reduce trophoblast invasion and spiral artery remodeling disrupt activin signaling in the decidual stroma. Studies in rodents and humans suggest that activin promotes decidualization and trophoblast invasion, therefore this may be a novel mechanism whereby bacteria can impair placentation. In addition to affecting stromal cell signaling and trophoblast function, they found that *in vivo* infection of macaque decidua and rat mesometria altered the activation state or proportion of uNK cells, respectively, without inflammation. These data suggest that Pg in the decidual stroma disrupts pathways important for cell differentiation and proliferation, and impacts non-immune functions of immune cells.

Intra-amniotic infection in extremely preterm birth was discussed by **Shigeru Saito**. Intra-amniotic infection is a major cause of preterm birth (PTB). Saito and colleagues established a new PCR method by which all the species of bacteria, Mycoplasma, Ureaplasma and fungi are detectable. As a result, PTB was classified into intra-amniotic infected PTB, sterile – inflamed PTB, and sterile– non-inflamed PTB. Antibiotics therapy was effective to prolong the gestational period in infected PTB, but did not prolong the gestational period in non-infected cases. 17 α -hydroxyprogesterone caproate could prolong the gestation in limited PTB cases with sterile-mild intra-amniotic inflammation.

3.3. Conclusion

This workshop provided insights into how different infectious agents affect placental biology, and therefore adversely affect pregnancy outcomes. Several common themes are starting to emerge regarding the impact of different infectious agents on the establishment of pregnancy; in particular, effects on EVT invasion, altered decidual leukocyte phenotypes and aberrant spiral artery remodeling. Discussion also centered around the best models to investigate some of the questions posed by the speakers, although no consensus was reached. In addition, it was noted that timing of infection during pregnancy may be critical for impacting pregnancy outcome. Further research is required to address these questions, but it is evident that based on timing and type of infection, different treatment strategies will need to be developed.

4. Gestational trophoblastic disease (GTD)

Chairs: Kazuhiko Ino and Eiko Yamamoto.

Speakers: Hiroshi Fujiwara, Kaoru Niimi, Hirokazu Usui, Eiko Yamamoto.

4.1. Outline

Gestational trophoblastic disease (GTD) is a group of diseases characterized by abnormal cellular proliferation of atypical trophoblasts, including hydatidiform mole, invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT) and epithelial trophoblastic tumor (ETT). Hydatidiform mole is an abnormal pregnancy caused by genetic fertilization disorders, which have higher potential to develop to gestational trophoblastic neoplasia (GTN) than normal trophoblasts. However, the involvement of the genetic origin of trophoblastic cells in the characteristics of GTN remains unclear. PSTT and ETT are rare tumors occurring from extravillous trophoblasts and have poor prognosis in metastatic cases because of low sensitivity to chemotherapy. Approximately 15% of choriocarcinomas become chemo-resistant and the factors for developing malignant potential of trophoblasts should be identified. In this workshop, novel therapeutic strategies for GTN in terms of management, diagnosis and treatment were discussed.

4.2. Summary

Eiko Yamamoto gave an overview of clinical features of gestational trophoblastic diseases in Japan. The registration data of gestational trophoblastic diseases in 1974–2015 showed that the incidence of hydatidiform mole was 1–3 per 1,000 live births in Japan. The incidence (per 100,000 live births) of invasive mole, choriocarcinoma and PSTT were 10–20, 1.9–5.5 and 0.1–0.9, respectively, in 1992–2015. The cure rate of choriocarcinoma was improved from 42% in the 1960s to 89.7% in the 2000s, and between these decades the proportion of hydatidiform mole in antecedent pregnancies of choriocarcinoma decreased from 40% to 24%. These results suggest that the registration system may be effective to improve the outcome of choriocarcinoma.

The cytogenetic classification of hydatidiform moles can be determined by DNA polymorphism analysis. **Hirokazu Usui** discussed how they have further applied this method to gestational trophoblastic disease. Using this approach, Usui and colleagues clarified the mitochondria origin of androgenetic complete hydatidiform mole. Second, they attempted to predict the efficacy of methotrexate to treat low-risk gestational trophoblastic neoplasia using methylenetetrahydrofolate reductase (MTHFR) polymorphisms. The MTHFR 677 TT genotype in molar tissue might be a predictive marker of the failure of methotrexate. Finally, they showed the existence of the gestational components of cell-free DNA in choriocarcinoma patients' plasma, which may be a more sensitive marker of choriocarcinoma than serum hCG.

Kaoru Niimi presented evidence that glycosyltransferases regulate

the malignant potential of trophoblasts. Core 2 β 1, 6-N acetylglucosaminyl transferase (C2GnT) catalyzes Core 2 structure on serine-linked oligosaccharides of human chorionic gonadotropin (hCG) and produces hyperglycosylated hCG. C2GnT was highly expressed in choriocarcinoma cells. Suppression of C2GnT reduced cell migration and invasive potential, and adhesion to HUVEC cells. Natural killer (NK) cells killed C2GnT knockout cells more efficiently than control cells. These findings suggest that choriocarcinoma cells may acquire a highly malignant potential by expressing C2GnT, and escape from the innate immune system by C2GnT-mediated glycosylation of MHC class I chain-related molecule A (MICA).

Hiroshi Fujiwara discussed the applicability of laeverin as a marker of PSTT. Fujiwara and colleagues produced monoclonal antibodies that react with human EVT and found a novel membrane-bound peptidase, named "laeverin", which is specifically expressed on EVT. Using anti-laeverin antibodies, they observed that laeverin was also expressed on PSTT that is considered to be derived from EVT at the implantation site. Since the expression of laeverin was specific to EVT-lineage cells, we propose that laeverin is a new marker of PSTT.

4.3. Conclusion

The aim of this workshop was to discuss how to cure 100% of GTDs. The registration system of GTDs is effective for decreasing choriocarcinoma that occurs after hydatidiform mole as well as understanding the features of GTDs. Cytogenetic analysis of molar tissue or patient's blood may be used to predict the effectiveness of the treatment for post-molar gestational trophoblastic neoplasia (GTN) and choriocarcinoma. GnT-IVa and C2GnT are new biomarkers of choriocarcinoma, especially for early diagnosis and poor prognosis of choriocarcinoma. Preventing escape from NK cell attack by suppressing C2GnT, may be a novel strategy for treatment of choriocarcinoma. In terms of PSTT, laeverin may contribute to the correct diagnosis of PSTT and a new treatment may be found using anti-laeverin antibody.

5. Drug delivery in pregnancy: overcoming problems and developing new technologies

Chairs: Lynda Harris and Masatoshi Tomi.

Speakers: Natalie Hannan, Lynda Harris, Sampada Kallol (presented on behalf of Christiane Albrecht), Takeshi Nagamatsu, Masataka Nomoto, Masatoshi Tomi.

5.1. Outline

The aim of this workshop was to raise awareness of the technical problems and barriers associated with drug delivery in pregnancy, and to discuss current advances in the field. The workshop was designed for delegates who are considering undertaking drug delivery-based research projects, and those who wish to troubleshoot current strategies.

5.2. Summary

Lynda Harris opened the workshop by giving an overview of methods for targeted drug delivery in pregnancy. To mitigate the risks associated with systemic administration of drugs in pregnancy, novel strategies are being developed that allow targeted delivery of payloads specifically to uterine and/or placental tissues, limiting transfer to the fetus. This is achieved by encapsulating drugs inside biocompatible nanoparticles and decorating their surface with targeting moieties such as peptides or antibodies. Targeted delivery offers enhanced drug efficacy, improved pharmacokinetics and reduced off target side effects. Dr Harris discussed the advantages and disadvantages of targeted delivery systems and reviewed current targeted approaches for inhibition of preterm labour, enhancement of placental function and uterine blood flow, and improved gene delivery.

Sampada Kallol introduced transport studies in human primary trophoblast cells. Investigations of placental drug and nutrient transporters revealed major differences in transporter expression and activity depending on the differentiation state of the trophoblast cells. The directionality of selected substrates (e.g. cholesterol) was further explored on confluent human primary trophoblast monolayers using Matrigel-coated Transwell® inserts. The results demonstrated a predominant apically (maternally) orientated cholesterol efflux, consistent with the localization of the cholesterol transporter ABCA1. These findings underline that human primary trophoblasts represent a highly physiological and suitable model for transport studies in term placenta.

Masatoshi Tomi discussed the physiological and pharmacological roles of organic anion transporter 4 (OAT4) in the placenta. Human OAT4 is localized at the basal plasma membrane of placental syncytiotrophoblasts. Because orthologs of human OAT4 are found in primates, but not in rodents, OAT4 is speculated to have some unique roles that cannot be clarified in rodents. Tomi and colleagues uncovered the role of placental OAT4 in estriol biosynthesis, which is unique to human and higher primates. Placental OAT4 mediates the uptake of 16 α -OH DHEAS- an estriol precursor. Additionally, OAT4 mediates the transport of angiotensin-II receptor blockers, which cause adverse pregnancy outcomes like oligohydramnios in humans.

Takeshi Nagamatsu introduced a drug delivery system to regulate placental transfer using nano-micelle technology. Medical application of nano-micelle technology is a promising strategy to concentrate drug distribution to target tissues. During pregnancy, drug selection is quite restricted due to concern for harmful effects on the fetus. Dr Nagamatsu discussed his current work using PEGylated-drug compounds, which spontaneously assemble into nano-micellar structures, to enhance uteroplacental drug targeting. He discussed the potential challenges of regulating placental transfer using drug-incorporated nano-micelles and the future possibility of their clinical application for perinatal diseases.

Masataka Nomoto gave an update on the search for therapeutic agents for fetal growth restriction (FGR). FGR is associated with neonatal morbidity and mortality, yet no effective treatment has been established. Based on preeclampsia research, Dr. Nomoto proposed that drugs altering the function of extravillous trophoblasts are a treatment for FGR. Nomoto and colleagues screened drugs for the ability to alter

trophoblast function, using drug repositioning strategies. The effects of a commercially available chemical library (about 1500 compounds) on BeWo cell proliferation, invasion, and placental growth factor production were investigated using cell culture-based assays. They identified multiple compounds that might regulate the function of trophoblasts. These drugs may be useful for elucidating the mechanism of diseases related to placental formation, such as FGR.

Finally, **Natalie Hannan** introduced esomeprazole as a novel therapeutic to treat preeclampsia. Preeclampsia is clinically characterized by new onset hypertension and either end organ damage or fetal growth restriction. There are currently no treatments for preeclampsia. Previously Hannan and colleagues discovered that the proton pump inhibitor, esomeprazole, can mitigate the pathophysiology of preeclampsia *in vitro*, *ex vivo* and *in vivo*. Together with clinical collaborators they assessed the potential of esomeprazole to treat preeclampsia in women with severe early onset (< 34 weeks gestation) in a Phase II clinical trial. They observed that daily esomeprazole (40 mg) did not prolong gestation in pregnancies with preterm preeclampsia, nor decrease circulating plasma soluble fms-like tyrosine kinase 1 levels. Higher levels in the maternal circulation may be needed for clinical effect especially as a treatment to alleviate pathology in this cohort of very sick women. A prospective trial to assess the ability esomeprazole to prevent preeclampsia in high risk women is currently underway.

5.3. Conclusions

It is evident that whilst the placental barrier acts effectively to facilitate hormone biosynthesis, nutrient partitioning, and to prevent toxic substances entering the fetal circulation, it represents both an exciting therapeutic target and a logistical challenge in terms of drug delivery in pregnancy. Numerous targeted approaches are being developed for selective delivery of therapies to the placenta and uterus, which offer enhanced drug efficacy, improved pharmacokinetics and reduced side effects. In parallel, the search continues to identify appropriate compounds to treat placental dysfunction and/or maternal symptoms that are both safe and effective.