Global Pregnancy Collaboration symposium on placental health: Summary and recommendations

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1. Introduction

The NIH recently emphasized the importance of the placenta by establishing the Human Placenta Project, a $40,000,000 venture to accelerate knowledge acquisition related to the human placenta. The goal is to increase understanding of the structure and function of the human placenta in real time, with the ultimate target to prevent and cure human disease. The Global Pregnancy Collaboration (CoLab) is an international consortium of centers sharing data and biological samples to facilitate studies to understand adverse pregnancy outcomes. In our annual meeting in 2015 the group sought to complement the current NIH directive with an interactive assessment of "Placental Health". The goal was to identify targets for mechanistic research, which is not currently

emphasized in the NIH Human Placenta Project. Particular attention was directed to what could be accomplished by a large consortium such as CoLab with abundant data and biological specimens. Further CoLab has the capacity to mount collaborative interactions and in particular rapidly accumulate new data and biological samples. All of these assets are directed toward the goal of CoLab, to reduce maternal and infant mortality. This goal mandates inclusion of investigators, materials and data from the settings in which these deaths predominantly occur, low and middle income countries.

The group met in Oxford in September 2015 for a two day session to consider research targets to facilitate the understanding of Placental Health. The meeting was highly interactive and in this summary we will attempt to distill the important points addressed, insights gained and suggested research directions. We briefly summarize the presentations, which is extended by selected in depth presentations of selected topics in accompanying manuscripts.

2. Presentations

The initial presentations dealt with the general assessment of placental health. The spectrum of approaches was addressed, from a discussion of classical pathological examination of the placenta to the evaluation of placental epigenetics. These two topics are addressed in detail in accompanying manuscripts.

3. Biological assessment of placental health

3.1. Morphology

Neil Sebire considered the value and limitations of morphological assessment. Even with its limitations this approach has defined different subsets of disease (e.g. early and late onset preeclampsia) and broadly characterized underling mechanisms.

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However, the potential value of this approach is limited by collection strategies and examinations directed by clinical considerations and by methodological issues. With clinical assessments, samples are evaluated with knowledge of the clinical indications for the examination, which results in substantial bias. Also the examination of reasonable numbers of truly normal placentas is mandatory for determining the meaning of findings in pathological settings. Clinically, what are considered as "normal" are very often placentas sent to pathology for a cause other than the one being investigated. This shortcoming is, of course, nearly insurmountable for controls for preterm delivery. Further, the frequency of lesions in the normal setting is under estimated because of the limited numbers of even these so called "normal" placentas that are examined. Methodologically, it is well established that there are appropriate approaches to obtain placentas necessary for examinations, both morphological evaluation and specialized evaluation, which are rarely realized with materials obtained clinically. Further, any placental sample is a very limited representation of the entire placenta and there are important differences in the site on the surface or the depth in the parenchyma that are never addressed in clinical care (or in many clinical studies). Thus, it is clear that research to understand the placenta with current but also with future strategies demands samples carefully collected with well-defined clinical diagnoses and appropriate controls and examination with the pathologist blinded to clinical outcome. Further recommendations are detailed later in this presentation and in Dr. Sebire's manuscript.

3.2. Epigenetic assessment

Daniel Vaiman in an accompanying presentation and manuscript examined one of the newest approaches to understanding placental health. He reviewed the current information on the effect of epigenetic modifications upon several aspects of placental function. For many years the mechanism of genetic regulation was addressed primarily as variants in sequence. Now is evident that non-transcriptional regulation, which has the potential to be regulated by environmental factors, is a major regulator with effects that can span generations. Approaches to this regulation involve histone modification, methylation and gene silencing by miRNAs. Histone regulation is difficult and expensive to study. Methylation is readily assessed but the relationship to gene expression whether increased or decreased is not always obvious. This has directed attention to miRNAs as a more easily measured and interpretable mechanism of epigenetic regulation. There is increasing evidence of the regulatory involvement of miRNA at multiple steps of placental development and function. The other cited mechanisms are also involved. Dr. Vaiman details regulation of immunity, invasion, proliferation and vasodilation by miRNAs. He also presents mechanisms by which these miRNA can be environmentally regulated and the established roles for certain specific miRNAs. It appears certain miRNA are associated with adverse pregnancy outcomes such as preeclampsia. This provides regulatory insights and potentially targets for therapy. The effects of miRNA are not only local but these molecules can also be found in the circulation indicating systemic effects. The presence of these miRNAs in the circulation suggests these may serve as potential biomarkers for adverse outcomes. He concludes with the potential role of using miRNA as therapeutic agents directed at modifying syncytial function.

3.3. Real time structure function studies

The next section addressed real time, structure function studies of placental health. The topics included an overview of the topic by Les Myatt, an in depth assessment of the potential of placental microvesicles by Dionne Tannetta and a brief description of CoLab's first efforts to use "big data" to address placental health by Annetine Staff.

Les Myatt began by addressing the rationale/importance of assessing placental health across gestation as a real-time indicator of normal fetal/placental growth and development. However, he also emphasized the long range implications of placental health for the health of the offspring in adulthood because of its impact on developmental programming. In reviewing the determinants of placental function he considered evaluation of these functions as markers of placental health. Factors considered were integrity of the placental barrier (physical and immune), uteroplacental and fetal-placental blood flows, and those affecting transport including placental size, in particular syncytiotrophoblast surface area, and expression of transporters. In addition, the synthetic function of the placenta both for fetal needs and fetal-maternal communications provides targets for assessment of placental health. He discussed monitoring techniques currently available for evaluating these functions, pointing out that the imaging technologies being emphasized in the NIH Human Placenta Project can accomplish some but not all of these goals. Basic science studies of the past 20 years have revealed the vast range of steroids and peptides produced by the placenta, however their utility for assessment of placental health has scarcely been investigated. He suggested that a useful strategy might be to consider revisiting older assessments of placental metabolic functions. As an example he reviewed the elegant pathway of placental estrogen production with the final product, estriol, dependent on maternal precursor and combined fetal and placental metabolism. Estriol concentrations in urine and maternal blood were used 40—50 years ago as a measure of fetal well-being before losing favor. He pointed out that applying current measurement techniques and evaluations of intermediate metabolism in this and other pathways might provide useful insights especially when coupled with greater awareness of the different clinical phenotypes underlying obstetric conditions.

While the recent explosion of interest in measurement of placental peptides such as PlGF, PAPP-A and CRH has not yielded clinically useful predictors of preeclampsia, it has provided evidence that these and other placental products may reflect placental health. The physical placental assessments to complement these will likely proceed rapidly because of the emphasis on these in the NIH placental project. He briefly reviewed the strengths and weakness of current technologies. The major imaging resource, sonography, effectively measures size, shape and anomalous implantation and can determine relative changes in blood flow. It cannot measure absolute blood flow or identify and evaluate what are perhaps the most important placental vessels, those in the terminal villi. Newer technology, MRI and PET, have the potential to measure perfusion and transport. Emerging technologies with great potential make use of non-invasive sampling of the placenta in real time coupled with cutting edge molecular and single cell techniques. One approach is sampling trophoblast cells shed into cervical mucous and another measuring placental components released into the maternal circulation as microvesicles. The potential of both of these is being closely examined in the NIH Human Placenta Project.

Nonetheless there are obstacles to success even as technology improves. Dr. Myatt pointed out the lack of large longitudinal studies supported by comprehensive and accurate clinical data. Such data is necessary for accurate phenotyping and to identify and control for confounding factors such as fetal sex, ethnicity, and environmental influences.

3.4. Placental microvesicles

Dionne Tannetta addressed the huge potential of studying placental fragments, syncytiotrophoblast extracellular vesicles (STBEV), as "circulating placental biopsies". This is one of the potential areas being examined in the NIH placental project but also one in which CoLab with its extensive serum/plasma samples might be especially helpful. It is useful as a technique to serially and minimally invasively evaluate placental heath. These vesicles can be demonstrated from 6 weeks of gestation. The vesicles come from the entire surface of the syncytiotrophoblast rather than a small area as is obtained from a placental biopsy. The components of the vesicle that can be studied are the surface of the vesicle in general (e.g. evidence of oxidative stress) or specifically (antigen expression), materials bound to the vesicle (e.g. angiogenic and anti-angiogenic factors) and materials within the vesicle, including proteins and RNA. The phospholipid bilayer protects low abundance biomarkers and those with a short half life making them much more amenable to study than soluble factors in blood. The vesicles are biologically active and serve as modifiers of immune function and endothelium and platelets with qualitative and quantitative changes in the presence of inflammation or placental vascular malperfusion. The changes with normal pregnancy and differences with "disease" can be evaluated longitudinally and repetitively to provide insights into normal physiological progression and the evolving natural history of disease. There are, however, still important questions to be answered as to turnover, routes of egress from the circulation and recognition of subtypes of STBEV. Also current techniques of separation and isolation by differential centrifugation are not practical because of the low abundance of STBEV.

Many of the challenges to be addressed have been explored with similar studies of microvesicles in association with cancer. Microvesicles appear to be involved in disease progression and metastasis. They are proposed as useful for screening, early diagnosis, prediction, prognosis and monitoring disease. This field is currently far ahead of efforts with STBEV and should provide insights into solutions to the challenges presented. These are discussed in detail in Dr. Tannetta's manuscript.

3.5. Big data

Annetine Staff presented an overview of an effort by CoLab to use big data to assess placental health. The hypothesis to be tested was that the angiogenic factor, PlGF, represents a marker for syncytiotrophoblast stress with associated placentally associated pregnancy complications rather than being solely a preeclampsia marker. In this study she and her colleagues invited investigators with published studies of angiogenic factors that had well characterized patient data to share their data. They studied 16,516 pregnancies from 23 cohorts. Two major challenges were encountered. The first was that the data was generated from several analytical platforms resulting in similar patterns but otherwise markedly disparate data. It was possible to combine these data with mathematical modeling such that the predictive power was at least as good as the individual data sets.

The second problem that was actually more difficult to resolve was the merging of outcome and demographic data from the different cohorts. Data from each of these cohorts was stored with different codes, formats and data fields that were extremely difficult to translate and combine. This stimulated an ongoing CoLab project, which will soon come to fruition, to prepare a state of art database with appropriate data fields in a common format that will be made available to investigators at either a nominal usage fee or gratis if funding of the project is not adequate (e.g. studies in low and middle outcome countries). We believe this will facilitate future data sharing (https://pregnancycolab.tghn.org/about/).

This study clearly demonstrates that merged biomarker data from multiple studies can improve statistical power sufficiently to address pathophysiology and possible subtypes of disease. It also illustrates challenges that must and can be overcome.

4. Placental stress and senescence

4.1. Cellular senescence

Lynn Cox introduced this topic with a presentation about cellular senescence. In the accompanying manuscript Dr. Cox presents an in depth discussion of cellular senescence, its genesis, effects and roles in normal physiology and pathophysiology. With senescence, which is essentially irreversible cell cycle arrest, there are characteristic morphological changes accompanied by altered gene expression. There is increased expression of genes that increase resistance to apoptosis as well as those that increase inflammatory activation. Dr. Cox details how cellular senescence may be necessary for some normal functions including wound healing, tissue remodeling and surveillance for malignancy but that premature senescence that can be activated by reactive oxygen species can lead to pathological changes.

With regard to pregnancy she points out that the process of syncytialization, mandatory to achieve a placental surface area sufficient for adequate nutrient and oxygen delivery, results in cellular senescence, which when it involves the maternal decidua, leads to the release of mediators which could contribute to the normal onset of labor. However, if this process were activated precociously the result could be premature labor. Syncytiotrophoblast or decidual senescence could be activated by the generation of reactive oxygen species secondary to the abnormal implantation accompanying preterm birth, preeclampsia, fetal growth restriction and stillbirth.

She outlines possible therapeutic interventions and encourages increased consideration of the implications of this process that has had little attention in reproductive studies.

4.2. Endoplasmic reticulum and mitochondrial stress

Graham Burton and Andrew Murray presented discussions of endoplasmic reticulum (ER) and mitochondrial stress at the conference. For the purposes of the Proceedings they merged their topics into a single attached manuscript, "Mitochondrial - Endoplasmic Reticulum Interactions in the Trophoblast: Stress and Senescence." They propose that endoplasmic reticulum and mitochondrial stress are inextricably linked functionally and structurally. The two organelles are physically connected through mitochondrial associated ER membrane (MAM) in a manner similar to synapses, with calcium exchange between the organelles linking their activities bidirectionally. As a result, mitochondrial and ER stress are closely interlinked, and each is unlikely to occur in isolation.

Oxidative stress, long associated with adverse pregnancy outcomes, is closely linked to mitochondrial stress. Not only do mitochondria contribute significantly to the generation of reactive oxygen species (ROS) that leads to oxidative stress, but ROS can also damage mitochondrial and other proteins. This can result in misfolding and loss of function, with disruption of energy generation subsequently further increasing ROS production. These events also influence endoplasmic reticulum function with the potential for a catastrophic feed-forward reaction. In the accompanying manuscript Drs. Burton and Murray provide an elegant overview of these phenomena, their consequences and potential protective mechanisms to prevent the catastrophe.

The authors discuss the unfolded protein response (UPR), which occurs similarly but with different mechanistic components in ER and mitochondria. The UPR is activated in response to cellular insults that result in misfolded and unfolded proteins exceeding the compartments folding capacity with potentially devastating consequences. One of the outcomes of the UPR is the selective cessation of non-essential protein synthesis in order to reduce further accumulation of unfolded proteins, and an increased synthesis of molecules that facilitate protein folding. In addition, some components of this response have been co-opted to serve other cellular functions resulting in diverse effects of the UPR.

The effect of endoplasmic reticulum and mitochondrial stress through the UPR on placental physiology and development is not always pathological. At low activity UPR may regulate cellular functional and homeostatic activities, including stem cell differentiation and antibody formation. Genetically knocking out components of the UPR response pathway results in abnormal placental structure in mice. However, with extensive activation there is resulting pathology. As the authors point out the boundary between physiology and pathology is blurred with these labels being at different ends of a spectrum.

Oxidative stress, ER stress and mitochondrial stress result in placental senescence characterized by cytological and metabolic changes and the release of proinflammatory cytokines and proteases. It is suggested that with advancing gestation and fetal and placental growth, the mismatch between maternal perfusion and fetal demands increases theses stresses leading to placental senescence. This progression may be accentuated and lead to disease in a setting of an excessive mismatch between maternal perfusion and fetal demands. These processes affect not only placental cells but also immune cells and the adjacent decidua. It is proposed that preeclampsia may be an exaggeration/acceleration of normal placental aging. The manuscript details the dangers of apoptosis in this setting and the protective mechanisms against these stresses.

4.3. Placental mitochondrial stress with obesity

Les Myatt reviewed the rising incidence of obesity in women of reproductive age and its linkage to adverse outcomes during pregnancy but also to programming of offspring for obesity, insulin resistance and cardiovascular disease in later life. Obesity is also a comorbid condition for gestational diabetes, a condition again associated with programming of the offspring. Further increasing maternal adiposity dramatically increases the risk for stillbirth. Dr. Myatt pointed out that one quarter of stillbirths, particularly those occurring in late gestation, are unexplained. He then described the "Director's" role of the placenta in gestation, controlling maternal metabolism and fetal growth and differentiation, and the pivotal role of mitochondria in placenta, being involved in steroid synthesis, calcium homeostasis, production of reactive oxygen species and amino acid transport in addition to their acknowledged role in ATP generation. He outlined the relationship of obesity to mitochondrial dysfunction in many tissues and presented his work showing an increase in placental oxidative stress and decrease in trophoblast mitochondrial respiration and ATP generation with increasing maternal adiposity. This difference is further exacerbated with gestational diabetes, however compensatory placental hypertrophy and increased glycolysis occur to perhaps compensate for the decreased oxidative metabolism and maintain pregnancy. He explained that despite this dramatic decrease in placental respiration and altered metabolism with obesity or gestational diabetes these pregnancies generally went to term with good fetal outcomes, suggesting there may still be enough placental reserve to support the fetus, but pointed out that the offspring may have been programmed for adult disease. He further offered the suggestion that in some instances the reserve might be exceeded or the placenta suffer another insult, which might then be associated with stillbirth towards term, the time when the majority of the unexplained stillbirths occur.

4.4. Term preeclampsia as a response to syncytiotrophoblast stress

Chris Redman considered the role of placental stress/senescence in adverse outcomes of later pregnancy. He presented an overview of the pregnancy problems that increase at term and post-term, including unexplained stillbirths, preeclampsia and eclampsia. Beyond term, acidemia and hypoxemia are more common in newborns even in the absence of labor. Before the widespread use of induction 40 years ago to prevent pregnancies from going beyond term, dysmaturity (fetal growth restriction at term) was more evident than now and seen as a dangerous clinical problem, labeled the Postmaturity Syndrome.

Placental histology at term changes and in apparently healthy women, resembles the pathology of preeclampsia, with increased intervillus fibrin, focal syncytial necrosis, microvillus loss and evidence of endoplasmic reticulum stress. Syncytial knots, which are a common feature of preeclampsia, increase with gestational age in apparently normal pregnancies. Previously these were categorized as a physiological marker of placental maturity. However, syncytial knots can be induced in placental explants by hypoxia or oxidative stress. Dr. Redman proposes they should be seen as markers of syncytiotrophoblast stress, intrinsic to changes imposed by increasing growth of the placenta in the constrained space of the uterus.

Circulating syncytiotrophoblast biomarkers give a different view of the same problem if they are interpreted for what they are, rather than for what clinicians would like them to be. Professor Redman and colleagues re-interpret them as markers of syncytiotrophoblast stress, usually hypoxic in origin. In studies *in vitro*, and in response to known stressors such as preeclampsia, s-Flt-1 and placental growth factor behave respectively as positive and negative stress markers of syncytiotrophoblast. In normal pregnancies, after 30 weeks, the observed changes in these factors (increasing s-Flt and decreasing PlGF) parallel *ex vivo* measurements of uteroplacental oxygenation that indicate increasing hypoxemia in both the umbilical vessels and intervillus blood. The reciprocally changing concentration of s-Flt and PlGF also correlate with reduced placental expression of the transcription factor GCM1 (glial cell missing-1) and syncytin-1, which promote syncytialization and are significantly reduced in hypoxia and with preeclampsia.

Professor Redman proposes that at and beyond term, placental growth compresses the villous tree such that perfusion of the intervillus space becomes limiting. The ensuing syncytiotrophoblast stress stimulates release of other syncytiotrophoblast stress proteins (e.g. activin A, inhibin A, corticotrophin releasing factor and leptin), all of which increase at term and increase further in preeclampsia. The eventual pregnancy outcome depends on the timing of spontaneous or indicated delivery. Women destined to develop preeclampsia may be classified as normal simply because delivery comes a few days earlier than the signs of preeclampsia. In other words the end of pregnancy is a race between a normal outcome and placental senescence leading to pathology including preeclampsia, late onset fetal growth restriction or stillbirth. He urges, similar to the recommendations of Dr. Cox, that this phenomenon of syncytiotrophoblast stress/senescence be considered and studied as the origin of pregnancy, especially late pregnancy, abnormalities.

5. Immunological influences on placental health

5.1. Regulation of trophoblast invasion

Ashley Moffett summarized the role of the uterine immune system in regulating placentation. Normal pregnancy occurs when the placental trophoblast cells invade sufficiently to transform the spiral arteries so that they are converted to high conductance vessels right until the end of gestation. Both under- and over-invasion of trophoblast result in pregnancy disorders: deficient invasion is the underlying problem in the Great Obstetric Syndromes (preeclampsia, growth restriction, stillbirth and preterm labor) while over-invasion results in placenta increta/percreta. There is evidence that the immune system subtly determines the depth of invasion. Her group developed this hypothesis because the site where the placenta implants into the uterus is the boundary between two genetically different individuals. The decidua basalis is densely populated by a unique type of lymphocyte, uterine Natural Killer (uNK) cells that can recognize and respond to paternally-derived HLA-C molecules using Killer Immunoglobulin-like receptors (KIR). KIR and HLA are the most highly polymorphic gene families in humans, defining an individual as self. This means that particular combinations of maternal KIR and fetal (paternal) HLA-C genotypes characterize each pregnancy. Certain combinations are associated with an increased risk of preeclampsia where the signal to the uNK cell is strongly inhibitory. In contrast, in pregnancies with large babies the maternal KIR/fetal HLA-C combinations would give a more activating signal to uNK. Research on these interactions will increase understanding of both the diseases of underperfusion and overperfusion including reduced and excessive fetal growth.

6. Summary

Fig. 1 illustrates factors involved in normal and abnormal placental functional development. The important pathological functional changes in the placenta are largely due to aberrations in normal processes dictating normal placental development. These can be present in excess (e.g. oxidative, endoplasmic reticulum or mitochondrial stress) or inappropriately timed leading to premature senescence. The excessive or untimely expression of these signals is influenced by the several processes described in the Workshop. These include environmental factors, such as obesity, poor diet, etc. The challenge is to identify the full range of these abnormalities with improved and innovative placental assessment directed at mechanisms to eventually guide therapy.

7. Recommendations

The following recommendations are based upon the material presented at the meeting and subsequent discussions. Recommendations are for the research community at large and where appropriate stress the role of large data and biobanks such as CoLab.

It is apparent that advances in the understanding of processes associated with placental health and dysfunction and the ability to assess these phenomena have increased rapidly. It is likely that continuing efforts to understand and detect these processes will greatly augment the largely observational efforts of the NIH Human Placenta Project.

1. *Mechanistic studies of placental health are a necessary complement to even state of the art observational studies.*

There are several general considerations to improve placental research that are common to all of these research strategies. Studies to understand placental health can rarely obtain adequate demographic and clinically relevant data, samples or appropriate controls relying on materials collected for clinical purposes. Neal Sebire elegantly describes this for morphological studies but the same arguments are pertinent for functional studies.
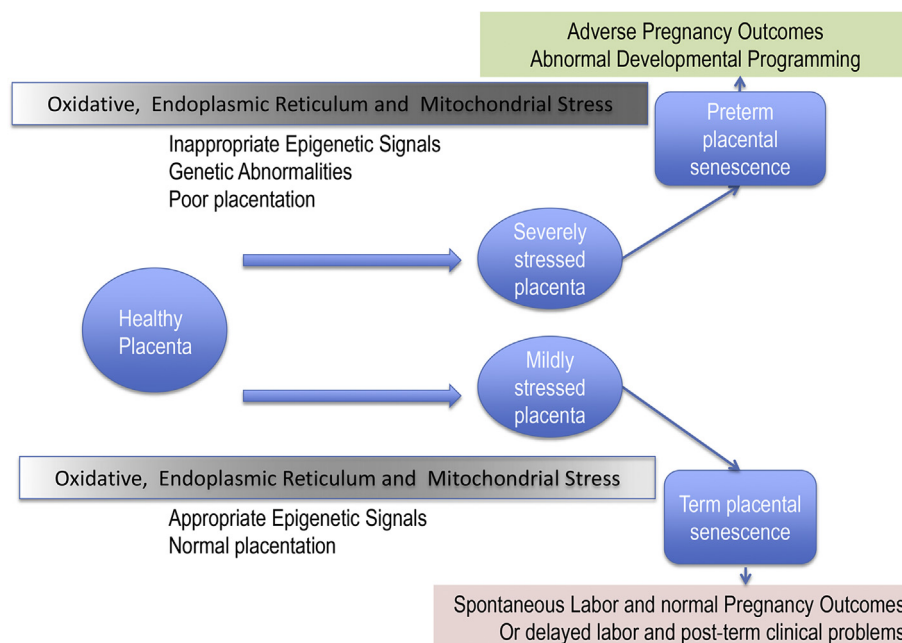
Fig. 1. Factors involved in normal and abnormal placental functional development. The important functional changes in the placenta are largely due to premature senescence, that is, an acceleration of normal processes that lead to placental stress. The excessive or untimely expression of these signals is influenced by the several processes described in the Workshop that comprise environmental factors, such as poor diet, obesity, smoking etc. resulting in excessive oxidative, endoplasmic reticulum or mitochondrial stress. The challenge is to identify the full range of these abnormalities with improved and innovative placental assessment directed at mechanisms to eventually guide therapy.

2. *Understanding placental structure and function requires samples carefully collected for research purposes that include clear descriptions of collection sites, timing and preservation strategies, the presence and absence of exposure to labor, adequate clinical data and a sufficient number of appropriate controls similarly collected. In all studies the investigators should be blinded to clinical data. An important strategy to begin would be a study funded to have as at least part of the study goal, the acquisition of excellently collected samples and data banked for future studies. A role served by CoLab could be to complement these collections with similarly collected very rare placental samples (e.g. premature placentas without premature labor) using the resources of the 36 member cohorts. In keeping with the mission of CoLab to improve health in low resource countries, these collections should also be done with identical strategies in these settings.*

Much useful information for understanding placental health and recognizing dysfunction will come from the imaging and observational studies of the NIH Human Placenta Project. There are certain areas that we consider especially promising and that would benefit from detailed study. Microvesicles offer the many advantages described by Dionne Tannetta but some key information and strategies are required to make these fully usable. The use of placental cells from cervical mucus was not discussed at length but it is likely that similar in depth studies are necessary to validate and maximize their value.

3. *New isolation techniques should be sought that will permit expansion of the studies of microvesicles to larger numbers of subjects and that could eventually make this a clinically useful diagnostic strategy. Also better understanding of how these particles are handled (half life, metabolism, routes of egress) is needed and can be guided by the rapid progress in the understanding of the role microvesicles being acquired in cancer research. When isolation strategies allowing the analysis of large numbers of samples are available CoLab should work to provide such samples from high income and low and middle income countries.*

Discussions of biomarkers of placental health in the presentations reveal several important points. Biomarkers to predict preeclampsia have not proven useful. It is also evident that biomarkers being assessed are indicators of placental health or disease and not specifically preeclampsia. It seems likely that measures of placental metabolic function, which are more sensitive than merely how much of a given material is produced by the placenta, could be valuable. It should also be worthwhile to measure materials produced by pathophysiological processes known to be relevant to placental dysfunction. Similarly, understanding of the proximal determinants of placental health, the immunological control of implantation and epigenetic modification of placental structure/function will provide other potential targets for biomarker assessment.

4. *Real time assessment of placental health or disease should be guided by understanding of the processes involved in normal placental implantation, growth and function as well as markers of pathophysiological functions demonstrated to be important in placental disease. It is worth reconsidering assessment of placental metabolic function with newer state of the art concepts and techniques. CoLab should be a source of materials for these studies.*

Studies of normal and pathophysiological processes indicate that these are often part of a spectrum ranging from normal to abnormal. Rarely are processes involved in dysfunction including oxidative, endoplasmic reticulum and mitochondrial stress and cellular senescence exclusively pathological. This recognition should guide studies of placental health and disease.

5. *Studies of placental health and disease should be guided by a precise understanding of normal and important placental mechanisms that may, in some settings, become dysfunctional. Research should be directed to how these factors promote disease in terms of their temporal or spatial distributions, or of their degree of activation. It is clearly a task for "big science" to identify these important cusps and CoLab should facilitate such studies.*

Perhaps the most important organ to lifelong health is the placenta. Understanding the processes involved in normal placental development and how they go awry and the diagnostic power to differentiate normal from abnormal will have a major impact on human health.