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Current approaches and developments in transcript profiling of the human placenta

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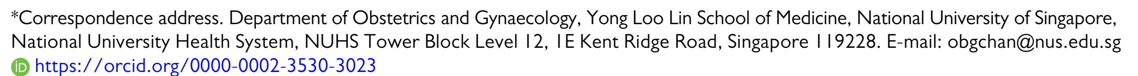

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Antenatal depression
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BACKGROUND: The placenta is the active interface between mother and foetus, bearing the molecular marks of rapid development and exposures *in utero*. The placenta is routinely discarded at delivery, providing a valuable resource to explore maternal-offspring health and disease in pregnancy. Genome-wide profiling of the human placental transcriptome provides an unbiased approach to study normal maternal–placental–foetal physiology and pathologies.

OBJECTIVE AND RATIONALE: To date, many studies have examined the human placental transcriptome, but often within a narrow focus. This review aims to provide a comprehensive overview of human placental transcriptome studies, encompassing those from the cellular to tissue levels and contextualize current findings from a broader perspective. We have consolidated studies into overarching themes, summarized key research findings and addressed important considerations in study design, as a means to promote wider data sharing and support larger meta-analysis of already available data and greater collaboration between researchers in order to fully capitalize on the potential of transcript profiling in future studies.

SEARCH METHODS: The PubMed database, National Center for Biotechnology Information and European Bioinformatics Institute dataset repositories were searched, to identify all relevant human studies using 'placenta', 'decidua', 'trophoblast', 'transcriptome', 'microarray' and 'RNA sequencing' as search terms until May 2019. Additional studies were found from bibliographies of identified studies.

OUTCOMES: The 179 identified studies were classifiable into four broad themes: healthy placental development, pregnancy complications, exposures during pregnancy and *in vitro* placental cultures. The median sample size was 13 (interquartile range 8–29). Transcriptome studies prior to 2015 were predominantly performed using microarrays, while RNA sequencing became the preferred choice in more recent studies. Development of fluidics technology, combined with RNA sequencing, has enabled transcript profiles to be generated of single cells throughout pregnancy, in contrast to previous studies relying on isolated cells. There are several key study aspects, such as sample selection criteria, sample processing and data analysis methods that may represent pitfalls and limitations, which need to be carefully considered as they influence interpretation of findings and conclusions. Furthermore, several areas of growing importance, such as maternal mental health and maternal obesity are understudied and the profiling of placentas from these conditions should be prioritized.

WIDER IMPLICATIONS: Integrative analysis of placental transcriptomics with other 'omics' (methylome, proteome and metabolome) and linkage with future outcomes from longitudinal studies is crucial in enhancing knowledge of healthy placental development and function, and in enabling the underlying causal mechanisms of pregnancy complications to be identified. Such understanding could help in predicting risk of future adversity and in designing interventions that can improve the health outcomes of both mothers and their offspring. Wider collaboration and sharing of placental transcriptome data, overcoming the challenges in obtaining sufficient numbers of quality samples with well-defined clinical characteristics, and dedication of resources to understudied areas of pregnancy will undoubtedly help drive the field forward.

Key words: placenta / decidua / transcriptome / microarray / RNA sequencing / pregnancy / trophoblast / development / pre-eclampsia

Introduction

The human placenta undergoes rapid growth and development usually over a span of 9 months. Serving as the maternal–foetal interface, the placenta facilitates communication between mother and child throughout gestation. Therefore, investigating the placenta provides a window into how the pregnancy has progressed and an insight into the potential health trajectory of the child. To better understand maternal–placental–foetal health, especially in the context of pregnancy complications, numerous microarrays and RNA-sequencing studies have been performed to profile the placental transcriptome. Recent rapid technological advancements in 'omics' have enabled parallel gathering of large datasets from maternal, placental and foetal tissues across gestation.

This review summarizes genome-wide human placental transcriptome studies performed over the last two decades. We provide an overview of transcriptome study methods, outline the important considerations for study design and interpretation, discuss past study

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results and highlight knowledge gaps that should be addressed in future studies. As the review is focussed on human placental studies, animal studies will not be referred to. Studies in other mammals (Barreto *et al.*, 2011; Buckberry *et al.*, 2017; Carter, 2018) have undoubtedly provided additional valuable perspectives on placental health and disease and have added to knowledge on comparative placentation across species.

Transcript profiling methods

Two methods used to obtain genome-wide placental transcript profiles are microarrays and RNA sequencing. These high-throughput technologies generate large amounts of data and offer a means to analyse the placenta in an unbiased manner.

Microarrays

Microarrays utilize short oligonucleotide probes embedded on a chip, which when hybridized to specific RNA or DNA sequences present in the sample emits fluorescence (Cox *et al.*, 2015), allowing simultaneous quantitation of many gene transcripts. Commercially available chips from Affymetrix, Agilent and Illumina are commonly used in placental research, although a few studies have custom-made theirs. The main drawback of microarray chips is that a gene-specific probe must be present for a gene to be detected. As the earliest placental microarray studies were performed around the time the first human genome was sequenced, not all transcripts were detectable by gene probes available at that time. Moreover, RNA biology was not as well understood as it is now with the current knowledge of non-coding RNA and RNA gene silencing. Additionally, microarray probes are species-specific. Nevertheless, given established bioinformatics pipelines and readily available statistical tools to analyse microarray data, with publically available datasets for comparison from the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) and the European Bioinformatics Institute (EBI) ArrayExpress repositories, microarrays continue to be widely used (Cox *et al.*, 2015).

RNA sequencing

Next-generation RNA sequencing is more sensitive than conventional microarray and generates a fuller picture of the placental transcriptome. The Illumina Hiseq and Genome Analyzer II systems are the most popular platforms in placental research and are increasingly used as the price of sequencing falls. Sequencing can detect rare and novel RNA transcripts, identify single-nucleotide variants in both coding and non-coding RNA of all lengths, and is not species-dependent. Furthermore, recent development of microfluidics technology with RNA sequencing allows transcripts of individual cells to be determined, which was not previously possible (Hu *et al.*, 2018b). However, single-cell RNA sequencing of the syncytiotrophoblast, which forms the placental cellular barrier, remains a challenge since its large size and multi-nucleated nature does not permit its isolation with microfluidics technology. The targeted sequencing depth or number of reads sequenced per sample is dependent on experimental aims and design. For instance, the ENCODE guidelines recommend a minimum sequencing depth of 30 million reads for bulk RNA sequencing that is commonly used for differential gene expression analysis, while 10 000 to 50 000 reads per cell in single-cell sequencing are sufficient to classify cells in an unbiased manner (Haque *et al.*, 2017). Another question-dependent experimental design consideration is whether to sequence library preparations from ribosomal RNA (rRNA)-depleted total RNA (including non-coding RNA) or those enriched for mRNA transcripts by poly A+ selection. Given the vast potential of RNA sequencing, it is unsurprising that its use is growing exponentially in placental research.

Why profile the human placental transcriptome?

In most pregnancies, the villous placenta is genetically identical to the foetus and is the first foetal-placental tissue in direct contact with the maternal exposome. The placental transcriptome may, therefore, represent to an extent both inherent foetal characteristics and the foetal response to the intrauterine environment. Data generated from genome-wide profiling of the human placenta have several uses. Firstly, analyses of normal placentas throughout gestation enhances understanding of healthy development, which serves as a reference point for studies of how the placenta responds and adapts to various exposures and challenges in complicated pregnancies. Secondly, by analysing placentas from compromised pregnancies, pathological changes linked with different clinical phenotypes can be identified and utilized for developing biomarkers or targets for prediction, diagnosis and therapeutic interventions. For instance, placental-specific gene products that are secreted into the maternal circulation can serve as a non-invasive direct readout of placental function and an indirect measure of foetal wellbeing (Cox *et al.*, 2015). One such success story of transcript profiling is sFLT1, which was first identified to be up-regulated in pre-eclamptic placentas by microarray (Maynard *et al.*, 2003) and is now being trialled in clinical screening to predict if a pregnant woman is at risk of developing pre-eclampsia (Zeisler *et al.*, 2016). Additionally, knowledge of the dysfunctional molecular processes at the maternal–foetal interface provides novel insights into the potential causal mechanisms underlying placental pathologies, which may open up new avenues for developing preventative measures for pregnancy complications. Moreover, the placenta functions as the intermediary between mother and child, participating in the normal programming of the developing foetus to face the prevailing environmental conditions of *ex utero* life (Burton *et al.*, 2016). Understanding these programming mechanisms and deviations in pathological conditions opens up the possibility of modifying offspring growth and health trajectories arising from compromised intrauterine environments, through interventions that target the placenta, or identifying at-risk children who will benefit from close follow-up and early childhood interventions.

Placental transcriptome: search methods and study themes

The PubMed database and the NCBI GEO and EBI ArrayExpress repositories were used to identify relevant studies and human placental transcriptome datasets, respectively up to May 2019. Our search

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Table I Healthy placental development.

Year	Accession ID	Platform	Type	Tissue/cell	Sampling site	Total no.	Gestation	Purpose	Associated publications
Gestation-specific effects									
2008	NCBI GEO GSE9984	Affymetrix Human Genome U133 Plus 2.0 Array	Microarray	Tissue	Chorionic villi	12 −4 1st −4 2nd −4 3rd	1st, 2nd and 3rd trimester	Profile placenta across gestation	Mikheev *et al.* (2008)
2011	NCBI GEO GSE28551	ABI Human Genome Survey Microarray Version 2	Microarray	Tissue	Chorionic villi	37 −16 1st −21 3rd	1st and 3rd trimester	Assess placental development across gestation	Sitras *et al.* (2012)
2015	NCBI GEO GSE66302	Illumina HiSeq 2000 -poly A+ selection -mean sequencing depth ∼6M	RNA-seq	Tissue	Amnion, chorion, chorionic villi, decidua, umbilical cord	7 −2 1st −5 2nd	1st and 2nd trimester	Development from early to mid-pregnancy	Roost *et al.* (2015)
2016	NCBI GEO GSE75010	Affymetrix Human Gene 1.0 ST Array	Microarray	Tissue	Placenta biopsy (basal plate + chorionic villi)	157	3rd trimester	Identify markers of villous maturation (with histological data)	Leavey *et al.* (2017)
2017	NCBI GEO GSE98752	Illumina Genome Analyzer IIx -poly A+ selection -mean sequencing depth ∼28M	RNA-seq	Tissue	Chorionic villi	9 −4 1st −1 2nd −4 3rd	1st and 3rd trimester	Placental development across gestation (with linked methylation data)	Lim *et al.* (2017b)
2018	NCBI GEO GSE100051	Illumina HumanHT-12 V4.0 Expression Beadchip	Microarray	Tissue	Chorionic villi	54 −42 1st −7 2nd −5 3rd	1st, 2nd and 3rd trimester	Profile placenta across gestation	Soncin *et al.* (2018)
	Not publically available	Affymetrix Human Genome U133A Array	Microarray	Tissue	Chorionic villi	10 −5 1st −5 3rd	1st and 3rd trimester	Identify placental-specific transcripts in maternal blood	Tsui *et al.* (2004)
Cellular characterization and differentiation									
2008	NCBI GEO GSE10612	Affymetrix Human Genome U133A Array; Affymetrix Human Genome U133A 2.0 Array	Microarray	Sorted cell (flow cytometry/ magnetic bead)	Decidua	11	1st trimester	Characterize decidual macrophages	Gustafsson *et al.* (2008)

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Table I Continued

Year	Accession ID	Platform	Type	Tissue/cell	Sampling site	Total no.	Gestation	Purpose	Associated publications
2008	NCBI GEO GSE11510	Affymetrix Human Genome U133 Plus 2.0 Array	Microarray	Primary cell cultures	Amnion, chorionic plate, chorionic villi, decidua, umbilical cord	10	3rd trimester	Placental cell taxonomy	Kawamichi *et al.* (2010)
2013	NCBI GEO GSE44368	Affymetrix Human Gene 1.0 ST Array	Microarray	Primary cell cultures	Chorionic villi	18 −9 female −9 male	3rd trimester	Sexual dimorphism of trophoblast and endothelial cells	Cvitic *et al.* (2013)
2013	NCBI GEO GSE24268	Agilent-014850 Whole Human Genome Microarray 4 × 44K G4112F	Microarray	Sorted cell (flow cytometry)	Decidua	Pooled	1st trimester	Characterize decidual natural killer cells	Wang *et al.* (2014)
2015	NCBI GEO GSE59126	Affymetrix Human Genome U133A Array	Microarray	Primary cell cultures	Chorionic villi (1st trimester), chorionic plate (3rd trimester)	10 (pooled) −5 1st −5 3rd	1st and 3rd trimester	Compare 1st trimester trophoblast vs 3rd trimester endothelial degradome	Ghaffari-Tabrizi-Wizsy *et al.* (2014)
2015	NCBI GEO GSE57834	Affymetrix Human Gene Expression Array	Microarray	Sorted cell (flow cytometry)	Chorionic villi	5	1st trimester	Characterize trophoblast subpopulations in early pregnancy	James *et al.* (2015)
2017	EBI ArrayExpress E-MTAB-5517	Affymetrix Human Transcriptome Array 2.0	Microarray	Sorted cell (flow cytometry)	Decidua	6	3rd trimester	Characterize decidual T-cell populations	Powell *et al.* (2017)
2017	EBI EGA EGA-D00001003705 (access requires approval)	Illumina NextSeq 500 -mean sequencing depth ∼21 471 reads	RNA-seq	Single cell	Chorionic villi	8	3rd trimester	Characterize cells from term and early-onset pre-eclampsia-affected placentas	Tsang *et al.* (2017)
2018	NCBI GEO GSE79879	Illumina NextSeq 500 -poly A+ selection -mean sequencing depth ∼39M	RNA-seq	Sorted cell (flow cytometry)	Decidua	5 (pooled)	1st trimester	Profile decidual natural killer cell population with expanded memory in subsequent pregnancy	Gamliel *et al.* (2018)
2018	NCBI GEO GSE89497	Illumina HiSeq 4000 -mean sequencing depth ∼1M	RNA-seq	Single cell with pre-sorting (magnetic bead)	Chorionic villi (1st trimester), basal plate (2nd trimester)	8 −7 1st −1 2nd	1st and 2nd trimester	Characterize placental cell subpopulations	Liu *et al.* (2018)
2018	NCBI GEO GSE107824	Illumina HumanHT-12 V4.0 Expression Beadchip	Microarray	Primary trophoblast cell culture	Chorionic villi	11 −6 1st −3 2nd −2 3rd	1st, 2nd and 3rd trimester	Assess trophoblast differentiation across gestation	Soncin *et al.* (2018)

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Table I Continued

Year	Accession ID	Platform	Type	Tissue/cell	Sampling site	Total no.	Gestation	Purpose	Associated publications
2018	NCBI SRA PRJNA492324	Illumina NextSeq 500; Illumina HiSeq 2500 -poly A+ selection for tissue -mean sequencing depth ~23M for tissue and ~0.5M per cell	RNA-seq	Single cell and tissue	Chorionic villi, decidua	9	1st trimester	Characterize cells from the first-trimester maternal–foetal interface	Suryawanshi *et al.* (2018)
2018	EBI ArrayExpress E-MTAB-6678	Illumina HiSeq 2000 -mean sequencing depth ~1M	RNA-seq	Single cell with pre-sorting (flow cytometry)	Decidua	5	1st trimester	Characterize cells from the first-trimester maternal–foetal interface	Vento-Tormo *et al.* (2018)
2018	EBI ArrayExpress E-MTAB-6701	Illumina HiSeq 4000 -mean sequencing depth ~50 000 reads	RNA-seq	Single cell with pre-sorting (flow cytometry)	Chorionic villi, decidua	7	1st trimester	Characterize cells from the first-trimester maternal–foetal interface	Vento-Tormo *et al.* (2018)
2018	NCBI GEO GSE124282	Ion Torrent PGM -mean sequencing depth ~9M	RNA-seq	Primary trophoblast cell culture	Chorionic villi	8 –4 2nd –4 3rd	2nd and 3rd trimester	Assess trophoblast differentiation across gestation (with linked ChIP sequencing data)	Wang *et al.* (2019a)
Gene expression variation and regulation									
2006	NCBI GEO GSE4421	Stanford Functional Genomics Human cDNA Microarray	Microarray	Tissue	Amnion, basal plate, chorion, chorionic plate, chorionic villi, umbilical cord	19	3rd trimester	Examine gene expression variation within the placenta and between closely associated tissues	Sood *et al.* (2006)
2012	NCBI GEO GSE36828	Illumina HumanHT-12 V3.0 Expression Beadchip	Microarray	Tissue	Chorionic villi	48	3rd trimester	Examine relationship of placental gene expression with methylation	Turan *et al.* (2012)
2014	NCBI GEO GSE56524	Applied Biosystems 5500 × 1 Genetic Analyzer –mean sequencing depth ~40M	RNA-seq	Tissue	Whole placenta biopsy (basal plate + chorionic plate + chorionic villi)	10	3rd trimester	Identify imprinted genes in the placenta	Metsalu *et al.* (2014)

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Table I Continued

Year	Accession ID	Platform	Type	Tissue/cell	Sampling site	Total no.	Gestation	Purpose	Associated publications
2015	NCBI GEO GSE66622	Illumina Genome Analyzer IIx -poly A+ selection -mean sequencing depth ~3M	RNA-seq	Tissue	Chorionic villi	40	3rd trimester	Assess inter and intra-variation in placental transcriptome (African-American, European-American, South Asian and East Asian ancestry)	Hughes *et al.* (2015)
2017	NCBI GEO GSE77085	Illumina HiSeq 2500 -mean sequencing depth ~83M	RNA-seq	Tissue	Chorionic villi	16	3rd trimester	Identify gene co-expression patterns in normal term placenta	Buckberry *et al.* (2017)
2018	EBI ArrayExpress E-MTAB-6683	Affymetrix Human Gene 2.1 ST Array	Microarray	Tissue	Chorionic villi	8	1st trimester	Validate source and source-derived organoid	Turco *et al.* (2018)
2019	dbGaP Study Accession: phs001717.v1.p1 (access requires approval)	Illumina HiSeq2000 -poly A+ selection -mean sequencing depth unavailable	RNA-seq	Tissue	Chorionic villi	80	3rd trimester	Determine placental gene regulation (with linked genotyping and methylation data)	Delahaye *et al.* (2018)
2019	NCBI GEO GSE109120	Illumina NextSeq 500 -mean sequencing depth ~23M	RNA-seq	Tissue	Chorionic villi	39	1st trimester	Sex: males vs females	Gonzalez *et al.* (2018)
	Not publically available	Illumina Genome Analyzer IIx -poly A+ selection -mean sequencing depth ~56M	RNA-seq	Tissue	Amnion, chorion, basal plate	5 (pooled)	3rd trimester	Examine gene expression variation between placental-associated tissues	Kim *et al.* (2012)
	Not publically available	Illumina Genome Analyzer IIx -poly A+ selection -mean sequencing depth ~10M	RNA-seq	Tissue	Placenta biopsy (no details provided)	20	3rd trimester	Identify placental-enriched genes compared to other tissue types	Saben *et al.* (2014b)
	Not publically available	Illumina Hiseq 2500 –mean sequencing depth ~20M	RNA-seq	Tissue	Chorionic villi	159	3rd trimester	Determine expression quantitative trait loci in the placenta (with linked genotyping data)	Peng *et al.* (2017)

ChIP, chromatin immunoprecipitation; dbGaP, database for Genotypes and Phenotypes; EBI, European Bioinformatics Institute; EGA, European Genome-phenome Archive; GEO, Gene Expression Omnibus; M, million reads; NCBI, National Center for Biotechnology Information; SRA, sequence read archive.

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included terms such as 'placenta', 'decidua', 'trophoblast', 'transcriptome', 'microarray', 'RNA sequencing' and was refined by restricting only to human studies and genome-wide datasets. Additional studies were identified by references within articles.

We identified a total of 179 unique genome-wide datasets related to human placenta. These datasets collectively represent the genome-wide transcriptomes of around 3000 placentas since 2004. Most of these datasets were generated within the last five years, highlighting the rapid expansion of human placental transcriptome studies, with a clear preferential shift towards RNA sequencing from conventional microarrays in the field.

Placental transcriptome studies can broadly be divided into four main study themes: healthy placental development (Table I), pregnancy complications (Table II), exposures during pregnancy (Table III) and *in vitro* placental cultures (Table IV). The tables list studies in chronological order and studies with fewer than five samples are presented separately in Supplementary Table SI. Studies in each theme are summarized and discussed in the context of the following considerations.

Important considerations for placental transcriptome studies

Good study design is critical to harness the potential of genome-wide transcript profiling of the placenta. Key aspects to be considered in study design are subject recruitment, sample processing at delivery, transcript profiling and data analysis methods and data validation (Fig. 1), all of which may represent potential pitfalls and limit the validity of conclusions that can be drawn.

Subject recruitment

Two main points to consider in subject recruitment are selection criteria and sample size. Firstly, the selection process in case–control studies should ensure suitable controls are chosen to compare with pathological cases identified by well-defined and established clinical definitions. As will be discussed in subsequent sections, varied clinical criteria can impact study findings and reproducibility. Hence, a consensus about research definitions of common pregnancy complications should be reached to make full use of available resources. The selection process must also determine if variables, such as gestational age, sex, labour status, mode of delivery and treatment modalities, which are known to affect placental gene transcription, are part of the inclusion/exclusion criteria. Researchers should also recognize a caveat of sampling placenta from the first half of pregnancy, is that the pregnancy outcome of an electively terminated pregnancy cannot truly be guaranteed as healthy as the final outcome cannot be determined, thus interpretation of findings involving such samples must take this into account.

Secondly, inadequate sample size may affect statistical power and study reproducibility. Although the average number of placentas profiled in each study is $\sim$28, this is largely skewed by eight large studies of more than 100 placentas each. The median number of placentas profiled per study is merely 13 (interquartile range 8–29). It is noted that while around one in five studies used fewer than 10 placentas, a considerable number of these smaller studies were performed when the use of profiling technologies were in their infancy and they were valuable in providing an early proof of concept for application in the field. Nevertheless, meta-analysis may be a means to overcome the effects of sample size in some of these earlier studies and small studies of rare conditions. While the choice of study inclusion ultimately rests on the researchers performing the meta-analysis, we strongly recommend caution with including very small studies with fewer than five samples (Supplementary Table SI) as study batch effects are unlikely to be sufficiently corrected for in such cases. Hence, future studies should aim for much larger sample sizes that are adequately powered to answer the study question, to improve reproducibility and verify the findings of past studies going forward.

Sample processing at delivery

Another important factor is the placental sampling procedure at delivery. The region of the placenta to biopsy is dependent on the question asked (Fig. 2). For instance, studies addressing invasion of the extravillous trophoblast into the maternal decidua sample the basal plate (Winn *et al.*, 2009), while those investigating the maternal–foetal transfer across the syncytiotrophoblast would sample the villous placenta (Bari *et al.*, 2016). Unwanted variation may arise from inappropriate sampling of the placenta, such as non-removal of the decidua for studies of the villous placenta, inclusion of infarcted areas and insufficient cleaning to remove excess blood. Another consideration is the importance of multisite sampling of the same region as several studies established intra-placental variation of gene expression (Pidoux *et al.*, 2004; Hughes *et al.*, 2015). The ideal way is to run replicate samples of each placenta, although this may not always be practical given that the cost of genome-wide transcript profiling is still relatively high per sample. An alternative is to pool RNA from multiple sites of the region of interest for each placenta and to have a large enough number of different placentas, so as to ensure differential expression patterns identified are related to the condition studied, rather than normal intra- and inter-individual biological variability.

RNA integrity is also vital for proper interpretation of transcriptome data. RNA integrity is determined by measuring the 28S to 18S rRNA ratio or assessing the RNA integrity number (RIN) by a commercially available algorithm. Some placental RNA transcripts are more susceptible to degradation than others due to differences in post-transcriptional regulation (Reiman *et al.*, 2017). Rapidly degrading transcripts are enriched among those encoding membrane components or proteins with transporter function, while stable transcripts are primarily those involved in intracellular function (Reiman *et al.*, 2017). A major determinant of RNA integrity is the time taken to fully immerse in RNAlater or snap-freeze placental biopsies following delivery, which shows an inverse correlation with RIN values (Fajardy *et al.*, 2009; Jobarteh *et al.*, 2014). Biopsies are often rinsed in ice-cold buffer to remove maternal blood contamination prior to RNA preservation, but this step may also alter the transcript profile, particularly at the villous sprouts, which are transcriptionally sensitive to mechanical disturbances (Burton *et al.*, 2014). Storage length prior to RNA extraction may affect the RIN value as well, depending on preservation methods used (Martin *et al.*, 2017). Flash-frozen samples appear more sensitive to RNA degradation over a long period of storage, compared with RNAlater-preserved samples (Fajardy *et al.*, 2009; Martin *et al.*, 2017). Therefore, RNAlater-preservation is preferential for better placental RNA quality as compared to snap-freezing in liquid nitrogen (Wolfe *et al.*, 2014; Pisarska

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Table II Pregnancy complications.

Year	Accession ID	Platform	Type	Tissue/cell	Sampling location	Total no.	Gestation	Purpose	Associated publications
Pre-eclampsia									
2006	NCBI GEO GSE4707	Agilent-012391 Whole Human Genome Oligo Microarray G4112A	Microarray	Tissue	Chorionic villi	14 −4 C −5 EOPE −5 LOPE	3rd trimester	EOPE or LOPE vs controls	Nishizawa *et al.* (2007)
2007	EBI ArrayExpress E-MEXP-1050	Affymetrix GeneChip Human Genome Focus Array	Microarray	Tissue	Decidua	35 −17 C −16 PE −2 IUGR	3rd trimester	PE or IUGR vs controls	Eide *et al.* (2008)
2007	NCBI GEO GSE6573	Affymetrix Human Genome U133 Plus 2.0 Array	Microarray	Tissue	Decidua, placenta biopsy (no details provided)	20 (pooled) −10 C −10 PE	3rd trimester	PE vs controls	Herse *et al.* (2007)
2008	NCBI GEO GSE12767	Affymetrix Human Genome U133 Plus 2.0 Array	Microarray	Tissue	Chorionic villi	12 −8 C −4 PE	1st trimester	Subsequent PE vs controls	Founds *et al.* (2009)
2008	NCBI GEO GSE10588	Applied Biosystems Human Genome Survey Microarray Version 2	Microarray	Tissue	Chorionic villi	43 −26 C −17 PE	3rd trimester	PE vs controls	Sitras *et al.* (2009b)
2009	EBI ArrayExpress E-TABM-682	Illumina Human-6 v2 Expression BeadChip	Microarray	Tissue	Decidua	104 −58 C −37 PE −9 SGA	3rd trimester	PE or SGA vs controls	Loset *et al.* (2011)
2009	NCBI GEO GSE14722	Affymetrix Human Genome U133A Array; Affymetrix Human Genome U133B Array	Microarray	Tissue	Basal plate	23 −11 C −12 PE	3rd trimester	PE vs preterm controls	Winn *et al.* (2009)
2010	NCBI GEO GSE24129	Affymetrix Human Gene 1.0 ST Array	Microarray	Tissue	Chorionic villi	24 −8 C −8 PE −8 IUGR	3rd trimester	PE or IUGR vs controls	Nishizawa *et al.* (2011)
2010	NCBI GEO GSE25906	Illumina humanWG-6 V2.0 Expression Beadchip	Microarray	Tissue	Chorionic villi	60 −37 C −23 PE	3rd trimester	PE vs controls	Tsai *et al.* (2011)

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Table II Continued

Year	Accession ID	Platform	Type	Tissue/cell	Sampling location	Total no.	Gestation	Purpose	Associated publications
2011	NCBI GEO GSE22526	Operon Human Genome Array Ready Oligo Set version 2.1	Microarray	Tissue	Placenta biopsy (basal plate + chorionic villi)	15 −8 EOPE −7 LOPE	3rd trimester	EOPE vs LOPE	Junus *et al.* (2012)
2011	NCBI GEO GSE30186	Illumina HumanHT-12 V4.0 Expression Beadchip	Microarray	Tissue	Chorionic villi	12 −6 C −6 PE	3rd trimester	PE vs controls	Meng *et al.* (2012)
2012	NCBI GEO GSE25861	Affymetrix Human Genome U133 Plus 2.0 Array	Microarray	Sorted cells (magnetic beads)	Chorionic villi	9 −3 C −5 PE+IUGR −1 IUGR	3rd trimester	Placental endothelial cells in PE with IUGR vs preterm controls	Dunk *et al.* (2012)
2012	NCBI GEO GSE35574	Illumina HumanWG-6 V2.0 Expression Beadchip	Microarray	Tissue	Chorionic villi	86 −40 C −19 PE −27 IUGR	3rd trimester	PE or IUGR vs controls	Guo *et al.* (2013)
2013	NCBI GEO GSE44711	Illumina HumanHT-12 V4.0 Expression Beadchip	Microarray	Tissue	Chorionic villi	16 −8 C −8 EOPE	3rd trimester	EOPE vs preterm controls (with linked methylation data)	Blair *et al.* (2013)
2013	NCBI GEO GSE47187	Agilent-028004 SurePrint G3 Human GE 8 × 60K Microarray	Microarray	Tissue	Chorionic villi	10 −5 C −5 PE	3rd trimester	PE vs preterm controls	Song *et al.* (2013)
2013	NCBI GEO GSE43942	NimbleGen Homo sapiens HG18 090828 opt expr HX12 (12 × 135k)	Microarray	Tissue	Placenta biopsy (basal plate + chorionic villi)	12 −7 C −5 PE	3rd trimester	PE vs controls	Xiang *et al.* (2013)
2014	NCBI GEO GSE54618	Illumina HumanHT-12 V4.0 Expression Beadchip	Microarray	Tissue	Chorionic villi	24 −12 C −12 PE	3rd trimester	PE vs controls	Jebbink *et al.* (2015)
2015	EBI ArrayExpress E-MTAB-3265	Illumina HumanHT-12 V3.0 Expression BeadChip	Microarray	Tissue	Chorionic villi	22 −11 low −11 high	1st trimester	High risk vs low risk of PE (based on uterine artery Doppler resistance index)	Leslie *et al.* (2015)
2015	NCBI GEO GSE74341	Agilent-039494 SurePrint G3 Human GE v2 8 × 60K	Microarray	Tissue	Chorionic villi	25 −10 C −7 EOPE −8 EOPE	3rd trimester	EOPE or LOPE vs controls	Liang *et al.* (2016)

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Table II Continued

Year	Accession ID	Platform	Type	Tissue/cell	Sampling location	Total no.	Gestation	Purpose	Associated publications
2015	NCBI GEO GSE73374	Affymetrix Human Gene 2.0 ST Array	Microarray	Tissue	Whole placenta biopsy (basal plate + chorionic plate + chorionic villi)	36 −17 C −19 PE	3rd trimester	PE vs controls (with linked methylation data)	Martin *et al.* (2015)
2015	NCBI GEO GSE60438	Illumina HumanWG-6 V3.0 Expression Beadchip; Illumina HumanHT-12 V4.0 Expression Beadchip	Microarray	Tissue	Decidua	125 −65 C −60 PE	3rd trimester	PE vs controls	Yong *et al.* (2015)
2016	NCBI GEO GSE75010	Affymetrix Human Gene 1.0 ST Array	Microarray	Tissue	Placenta biopsy (basal plate + chorionic villi)	157 −77 C −80 PE	3rd trimester	PE vs controls (with linked methylation and histological data)	Leavey *et al.* (2016); Christians *et al.* (2017); Leavey *et al.* (2018); Benton *et al.* (2018); Gibbs *et al.* (2019)
2017	NCBI GEO GSE94643	Affymetrix Human Gene 2.0 ST Array	Microarray	Tissue	Decidua	8 −4 C −4 PE	3rd trimester	Decidualization in PE vs preterm controls	Garrido-Gomez *et al.* (2017)
2017	NCBI GEO GSE93839	Affymetrix Human Gene 2.0 ST Array	Microarray	Tissue (laser microdissected)	Placenta biopsy (basal plate + chorionic villi)	8 −4 C −4 PE	3rd trimester	Trophoblast populations in PE vs preterm controls	Gormley *et al.* (2017)
2017	NCBI GEO GSE99007	Agilent SurePrint G3 Human GE v3 8 × 60K Microarray	Microarray	Primary cell culture	Chorionic villi	7 −3 C −4 PE	3rd trimester	Fibroblasts from PE vs controls	Ohmaru-Nakanishi *et al.* (2018)
2017	EBI EGA EGA-D00001003705 (access requires approval)	Illumina NextSeq 500 -mean sequencing depth ∼21 471 reads	RNA-seq	Single cell	Chorionic villi	8 −4 C −4 PE	Late 2nd and 3rd trimester	EOPE vs controls	Tsang *et al.* (2017)
2018	NCBI GEO GSE96984	Agilent-078298 human ceRNA array V1.0 4X180K	Microarray	Tissue	Basal plate	7 −4 C −3 PE	3rd trimester	PE vs controls	Unpublished
2018	NCBI GEO GSE66273	Agilent-014850 Whole Human Genome Microarray 4 × 44K G4112F	Microarray	Tissue	Chorionic villi	17 −5 C −6 PE −6 PE + HELLP	3rd trimester	EOPE vs preterm controls	Than *et al.* (2018); Varkonyi *et al.* (2011)

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Table II Continued

Year	Accession ID	Platform	Type	Tissue/cell	Sampling location	Total no.	Gestation	Purpose	Associated publications
2019	NCBI GEO GSE102897	Agilent-078298 human ceRNA array V1.0 4X180K	Microarray	Tissue	Chorionic villi	12 (pooled in pairs) −6 C −6 PE	3rd trimester	PE vs controls	Hu *et al.* (2018a)
	Not publically available, but available on request	CapitalBio Genomewide Microarray	Microarray	Tissue	Chorionic villi	10 (pooled) −5 C −5 PE	3rd trimester	PE vs controls	Zhou *et al.* (2006)
	Not publically available	Affymetrix Human Genome U133 Plus 2	Microarray	Tissue	Placenta biopsy (no details provided)	5 −3 C −2 PE + IUGR	3rd trimester	PE with IUGR vs controls	Jarvenpaa *et al.* (2007)
	Not publically available	Operon Human Genome Array Ready Oligo Set version 2.1	Microarray	Tissue	Placenta biopsy (basal plate + chorionic villi)	36 −18 C −18 PE	3rd trimester	PE vs controls	Enquobahrie *et al.* (2008)
	Not publically available	Affymetrix Human Genome U133A Array	Microarray	Tissue	Placenta biopsy (basal plate + chorionic villi)	18 (pooled in groups of 3) −9 C −9 PE	3rd trimester	PE vs controls	Hoegh *et al.* (2010)
	Not publically available	Agilent Human Genome Microarray 4 × 44K	Microarray	Tissue	Chorionic villi	26 (pooled) −13 C −13 PE	3rd trimester	PE vs controls	Lee *et al.* (2010)
	Not publically available	Operon Human Genome Array Ready Oligo Set versions 2.1 and 2.1.1	Microarray	Tissue	Chorionic villi	35 −15 C (normal notch) −15 PE −5 non-normal notch	3rd trimester	PE vs controls (with Doppler findings)	Centlow *et al.* (2011)
	Not publically available	GE Healthcare Codelink Human Whole Genome Bioarrays	Microarray	Tissue	Placenta biopsy (basal plate + chorionic plate + chorionic villi)	20 −10 C −10 PE	3rd trimester	PE vs controls	Kang *et al.* (2011)
	Not publically available	Illumina HumanRef-12 v3 Expression BeadChip	Microarray	Tissue	Chorionic villi	12 −4 C −4 PE −4 PTL	3rd trimester	PE or PTL vs TNL (with linked miRNA data)	Mayor-Lynn *et al.* (2011)
	Not publically available	Illumina HiSeq 2000 -mean sequencing depth ∼38M	RNA-seq	Tissue	Placental biopsy (basal plate + chorionic plate + chorionic villi)	40 −8 C −8 LOPE −8 GDM −8 SGA −8 LGA	3rd trimester	LOPE, GDM, SGA or LGA vs controls	Sober *et al.* (2015)

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Table II Continued

Year	Accession ID	Platform	Type	Tissue/cell	Sampling location	Total no.	Gestation	Purpose	Associated publications
	Not publically available	Ilumina HiSeq 2000 -poly A+ selection -mean sequencing depth ~22M	RNA-seq	Tissue	Chorionic villi	30 −10 C −10 LOPE −10 GDM	3rd trimester	LOPE or GDM vs controls	Lekva *et al.* (2016)
	Not publically available	Ion Torrent PGM -poly A+ selection -mean sequencing depth ~30M	RNA-seq	Tissue	Decidua	9 −3 C −3 EOPE −3 LOPE	3rd trimester	EOPE or LOPE vs controls	Tong *et al.* (2018)
Intrauterine growth restriction/small for gestational age									
2007	EBI ArrayExpress E-MEXP-1050	Affymetrix GeneChip Human Genome Focus Array	Microarray	Tissue	Decidua	35 −17 C −2 IUGR −16 PE	3rd trimester	IUGR or PE vs controls	Eide *et al.* (2008)
2008	NCBI GEO GSE12216	ABI Human Genome Survey Microarray Version 2	Microarray	Tissue	Chorionic villi	16 −8 C −8 IUGR	3rd trimester	IUGR with placental insufficiency vs controls	Sitras *et al.* (2009a)
2009	EBI ArrayExpress E-TABM-682	Illumina Human-6 v2 Expression BeadChip	Microarray	Tissue	Decidua	104 −58 C −9 SGA −37 PE	3rd trimester	SGA or PE vs controls	Loset *et al.* (2011)
2010	NCBI GEO GSE24129	Affymetrix Human Gene 1.0 ST Array	Microarray	Tissue	Chorionic villi	24 −8 C −8 IUGR −8 PE	3rd trimester	IUGR or PE vs controls	Nishizawa *et al.* (2011)
2012	NCBI GEO GSE25861	Affymetrix Human Genome U133 Plus 2.0 Array	Microarray	Sorted cells (magnetic bead)	Chorionic villi	9 −3 C −1 IUGR −5 IUGR + PE	3rd trimester	Placental endothelial cells in IUGR with PE vs preterm controls	Dunk *et al.* (2012)
2012	NCBI GEO GSE35574	Illumina HumanWG-6 V2.0 Expression Beadchip	Microarray	Tissue	Chorionic villi	94 −40 C −27 IUGR −19 PE	3rd trimester	IUGR or PE vs controls	Guo *et al.* (2013)
2014	EBI ArrayExpress E-MTAB-1956	NimbleGen Human HG18 60mer 4 × 72K Expression Array	Microarray	Tissue	Chorionic villi	24 (pooled in groups of 3) −12 C −12 IUGR	3rd trimester	IUGR vs control	Madeleneau *et al.* (2015)

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Year	Accession ID	Platform	Type	Tissue/cell	Sampling location	Total no.	Gestation	Purpose	Associated publications
2017	NCBI SRA PRJNA358255	Illumina HiSeq 2500 -mean sequencing depth ~44M	RNA-seq	Tissue	Placenta biopsy (chorionic plate + chorionic villi)	200 −112 C −33 SGA −55 LGA	3rd trimester	SGA or LGA vs controls	Deyssenroth *et al.* (2017)
2018	NCBI GEO GSE100415	Affymetrix Human Gene 1.0 ST Array	Microarray	Tissue	Placenta biopsy (basal plate + chorionic villi)	20 −20 IUGR	3rd trimester	Normotensive suspected IUGR only (extension of earlier study comparing healthy controls and hypertensive suspected IUGR)	Gibbs *et al.* (2019) (extension of GSE75010)
2018	Available as supplementary data within journal article	Illumina HiSeq 2500 -poly A+ selection -mean sequencing depth ~13M	RNA-seq	Tissue	Placenta biopsy (basal plate + chorionic villi)	91 −66 C −25 IUGR	3rd trimester	IUGR vs controls in women with and without chemotherapy during pregnancy	Verheecke *et al.* (2018)
2019	EBI ENA PRJEB30656	Illumina HiSeq4000 -poly A+ selection -mean sequencing depth ~55M	RNA-seq	Tissue	Placenta biopsy (no details provided)	10 −5 C −5 IUGR	3rd trimester	IUGR vs controls	Majewska *et al.* (2019)
	Not publically available	Affymetrix U95A Microarray	Microarray	Tissue	Placenta biopsy (no details provided)	6 −3 C −3 IUGR	3rd trimester	IUGR vs controls	Roh *et al.* (2005)
	Not publically available	Affymetrix Human Genome U133 Plus 2	Microarray	Tissue	Placenta biopsy (no details provided)	5 −3 C −2 IUGR + PE	3rd trimester	IUGR with PE vs controls	Jarvenpaa *et al.* (2007)
	Not publically available	Affymetrix Human Genome U133A Array	Microarray	Tissue	Placenta biopsy (basal plate + chorionic villi)	8 −4 C −4 IUGR	3rd trimester	IUGR vs controls	McCarthy *et al.* (2007)
	Not publically available	Affymetrix Human Genome U133 Plus 2.0 Array	Microarray	Tissue	Placenta biopsy (chorionic plate + chorionic villi)	20 −10 C −10 IUGR	3rd trimester	IUGR vs preterm controls	Struwe *et al.* (2010)
	Not publically available	Affymetrix Human Genome U219 Array	Microarray	Tissue	Chorionic villi	15 −5 C −4 IUGR −6 macro	3rd trimester	IUGR or macro vs controls	Sabri *et al.* (2014)
	Not publically available	Illumina HiSeq 2000 -mean sequencing depth ~38M	RNA-seq	Tissue	Placental biopsy (basal plate + chorionic plate + chorionic villi)	40 −8 C −8 SGA −8 LGA −8 PE −8 GDM	3rd trimester	SGA, LGA or PE or GDM vs controls	Sober *et al.* (2015)

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Table II Continued

Year	Accession ID	Platform	Type	Tissue/cell	Sampling location	Total no.	Gestation	Purpose	Associated publications
Macrosomia/large for gestational age									
2017	NCBI SRA PRJNA358255	Illumina HiSeq 2500 -mean sequencing depth ~44M	RNA-seq	Tissue	Placenta biopsy (chorionic plate + chorionic villi)	200 −112 C −55 LGA −33 SGA	3rd trimester	LGA or SGA vs controls	Deyssenroth *et al.* (2017)
	Not publically available	Affymetrix Human Genome U219 Array	Microarray	Tissue	Chorionic villi	15 −5 C −6 macro −4 IUGR	3rd trimester	Macro or IUGR vs controls	Sabri *et al.* (2014)
	Not publically available	Illumina HiSeq 2000 -mean sequencing depth ~38M	RNA-seq	Tissue	Placental biopsy (basal plate + chorionic plate + chorionic villi)	40 −8 C −8 LGA −8 SGA −8 PE −8 GDM	3rd trimester	LGA, SGA, PE or GDM vs controls	Sober *et al.* (2015)
	Not publically available	Arraystar Human LncRNA Microarray V3.0	Microarray	Tissue	Placenta biopsy (basal plate + chorionic villi)	8 −4 C −4 macro	3rd trimester	Non-diabetes macro vs controls	Song *et al.* (2018)
Gestational diabetes mellitus									
2005	NCBI GEO GSE2956	Affymetrix Human U133 Array	Microarray	Tissue	Chorionic villi	15 −8 C −7 GDM	3rd trimester	GDM vs controls	Radaelli *et al.* (2003)
2015	NCBI GEO GSE70493	Affymetrix Human Transcriptome Array 2.0	Microarray	Tissue	Placenta biopsy (basal plate + chorionic villi)	55 −25 C −30 GDM	3rd trimester	GDM vs controls (with linked methylation data)	Binder *et al.* (2015)
	Not publically available	Operon Human Genome Array Ready Oligo Set version 2.1	Microarray	Tissue	Chorionic villi	40 −21 C −19 GDM	3rd trimester	GDM vs controls	Enquobahrie *et al.* (2009)
	Not publically available	Affymetrix Human U133 Array	Microarray	Tissue	Chorionic villi	20 −5 C −9 GDM −6 T1D	3rd trimester	GDM or T1D vs controls	Radaelli *et al.* (2009)
	Not publically available	Illumina HiSeq 2000 -mean sequencing depth ~38M	RNA-seq	Tissue	Placental biopsy (basal plate + chorionic plate + chorionic villi)	40 −8 C −8 GDM −8 PE	3rd trimester	GDM, PE, SGA or LGA vs controls	Sober *et al.* (2015)

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Year	Accession ID	Platform	Type	Tissue/cell	Sampling location	Total no.	Gestation	Purpose	Associated publications
						−8 SGA −8 LGA			
	Not publically available	Affymetrix HuGene ST 1.0 Array	Microarray	Tissue (laser microdissected)	Placenta biopsy (no details provided)	12 −4 lean C −4 GDM −4 obese	3rd trimester	GDM vs obese non-diabetic vs lean controls	Bari *et al.* (2016)
	Not publically available	Illumina HiSeq 2500 -poly A+ selection -mean sequencing depth ∼20M	RNA-seq	Tissue	Placenta biopsy (no details provided)	54 −26 C −28 GDM	3rd trimester	GDM vs controls (with linked miRNA data)	Ding *et al.* (2018)
	Not publically available	Ilumina HiSeq 2000 -poly A+ selection -mean sequencing depth ∼22M	RNA-seq	Tissue	Chorionic villi	30 −10 C −10 GDM −10 LOPE	3rd trimester	GDM or LOPE vs controls	Lekva *et al.* (2016)
	Not publically available, but available on request	Illumina NextSeq 500 -mean sequencing depth ∼38M	RNA-seq	Tissue	Placenta biopsy (chorionic plate + chorionic villi)	12 −6 C −6 diabetic (GDM or T2D)	3rd trimester	Diabetes during pregnancy (GDM and T2D) vs controls (with linked methylation data)	Alexander *et al.* (2018)
Antenatal infections and inflammation									
2007	NCBI GEO GSE7586	Affymetrix Human Genome U133 Plus 2.0 Array	Microarray	Tissue	Chorionic villi	20 −5 C (never) −10 active −5 past	3rd trimester	Active placental malaria vs controls	Muehlenbachs *et al.* (2007)
2009	EBI ArrayExpress E-TABM-577	Affymetrix Human Genome U133 Plus 2.0	Microarray	Tissue	Chorionic villi	20 −10 C −10 PI	3rd trimester	Idiopathic PI vs controls	Kim *et al.* (2009)
2015	NCBI GEO GSE68474	Illumina HumanHT-12 WG V4.0 Expression Beadchip	Microarray	Tissue	Placental biopsy (basal plate + chorionic villi)	11 −5 C −6 PI	3rd trimester	Chronic PI vs controls	Raman *et al.* (2015)
2016	NCBI GEO GSE73712	Illumina HiSeq 2500 -mean sequencing depth ∼34M	RNA-seq	Tissue	Chorionic villi, decidua	15 −5 C −5 PI −5 iPTB	3rd trimester	Preterm with PI or preterm without PI vs controls	Ackerman *et al.* (2016)
2018	NCBI GEO GSE107376	Illumina HiSeq 2500	RNA-seq	Tissue	Placenta biopsy (basal plate +	18 (pooled in pairs)	3rd trimester	TrypC+ vs controls	Juiz *et al.* (2018)

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Table II Continued

Year	Accession ID	Platform	Type	Tissue/cell	Sampling location	Total no.	Gestation	Purpose	Associated publications
		-mean sequencing depth ~30M			chorionic plate + chorionic villi)	−12 C −6 TrypC+			
Labour									
2009	NCBI GEO GSE18809	Affymetrix Human Genome U133 Plus 2.0 Array	Microarray	Tissue	Chorionic villi	10 −5 TSL −5 PTSL	3rd trimester	PTSL vs TSL	Chim *et al.* (2012)
2009	NCBI GEO GSE18850	Affymetrix Human Genome U133 Plus 2.0 Array	Microarray	Tissue	Chorionic villi	10 −5 TNL −5 TSL	3rd trimester	TSL vs TNL	Chim *et al.* (2012)
2016	NCBI GEO GSE73685	Affymetrix Human Gene 1.0 ST Array	Microarray	Tissue	Amnion, chorion, decidua, placenta biopsy (no details provided)	21 −7 TNL −5 TL −7 PTNL −2 PTL	3rd trimester	Preterm vs term with and without labour	Bukowski *et al.* (2017)
2017	EBI ArrayExpress E-MTAB-5353	Illumina Human HT-12 WG V4.0 Expression Beadchip	Microarray	Tissue	Decidua	36 −11 TNL −8 TL −10 PTL −7 PTNL	3rd trimester	Preterm vs term with and without labour	Rinaldi *et al.* (2017)
	Not publically available	Illumina HumanRef-12 v3 Expression BeadChip	Microarray	Tissue	Chorionic villi	12 −4 TNL −4 PTL −4 PE	3rd trimester	PTL or PE vs TNL (with linked miRNA data)	Mayor-Lynn *et al.* (2011)
Recurrent miscarriage									
2010	NCBI GEO GSE22490	Affymetrix Human Genome U133 Plus 2.0 Array	Microarray	Tissue	Placenta biopsy (chorionic villi + basal plate)	10 −6 C −4 RM	1st and 2nd trimester	RM vs controls	Rull *et al.* (2013)
2016	NCBI GEO GSE76862	Affymetrix GeneChip Human Transcriptome Array 2.0	Microarray	Primary cell culture	Chorionic villi	Not stated (pooled into 6 groups of 3 to 5 samples)	1st trimester	Placental trophoblast cells from RM vs controls	Tian *et al.* (2016)
2018	NCBI GEO GSE121950	Illumina HiSeq 2000	RNA-seq	Tissue	Chorionic villi	6 −3 C	1st trimester	RM vs controls	Huang *et al.* (2018)

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Table II Continued

Year	Accession ID	Platform	Type	Tissue/cell	Sampling location	Total no.	Gestation	Purpose	Associated publications
		-mean sequencing depth ∼110M				−3 RM			
2018	NCBI GEO GSE113790	Illumina Hiseq 2000 -poly A+ selection -mean sequencing depth ∼49M	RNA-seq	Tissue	Decidua	6 −3 C −3 RM	1st trimester	RM vs controls (with linked methylation data)	Yu *et al.* (2018)
	Not publically available	Illumina HiSeq 2000 -mean sequencing depth ∼44M	RNA-seq	Tissue	Chorionic villi	10 −8 C −2 RM	1st trimester	RM vs controls	Sober *et al.* (2016)
Chromosomal abnormalities									
2015	NCBI GEO GSE70102	Affymetrix Human Genome U133 Plus 2.0 Array	Microarray	Tissue	Basal plate	20 −4 C −4 T13 −4 T18 −4 T21	2nd trimester	Aneupoidy vs controls	Bianco *et al.* (2016)
	Not publically available	Affymetrix GeneChip Human Genome U133 Plus 2.0 Array	Microarray	Tissue	Chorionic villi	18 −12 C −6 T21	1st trimester	T21 vs controls	Lim *et al.* (2017a)
Intrahepatic cholestasis of pregnancy									
2013	NCBI GEO GSE46157	Agilent-026652 Whole Human Genome Microarray 4 × 44K v2	Microarray	Tissue	Chorionic villi	30 (pooled into groups of 5) −10 C −20 IHCP	3rd trimester	IHCP vs controls	Du *et al.* (2014)

C, control; ENA, European Nucleotide Archive; EOPE, early-onset pre-eclampsia; GDM, gestational diabetes mellitus; HELLP, haemolysis, elevated liver enzymes, low-platelet count syndrome; IHCP, intrahepatic cholestasis of pregnancy; iPTB, idiopathic preterm birth; IUGR, intrauterine growth restriction; LGA, large for gestational age; LOPE, late-onset pre-eclampsia; macro, macrosomia; miRNA, microRNA; PE, pre-eclampsia; PI – placental inflammation; PTL, preterm labour; PTNL, preterm no labour; PTSL, preterm spontaneous labour; RM, recurrent miscarriage; SGA, small for gestational age; T13, trisomy 13; T18, trisomy 18; T21, trisomy 21; T1D, type 1 diabetes; T2D, type 2 diabetes; TL, term labour; TNL, term no labour; TSL, term spontaneous labour; TrypC+, *Trypanosoma cruzi* seropositive.

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et al., 2016). However, if the sample is limited and there are plans to utilize the tissue for other types of analysis, a potential drawback is that preservation in RNAlater, which has a high salt content and denatures proteins, may interfere with future analysis of native proteins and other techniques. Therefore, researchers should ideally work as efficiently as possible with RNase-free equipment and consumables while handling the placenta, although it is ultimately up to the researcher how they wish to process and store their placental samples.

Transcript profiling and data analysis methods

Following sample collection, various RNA isolation and possibly enrichment methods may be required, depending on which RNA species (e.g. long non-coding RNA or mRNA) are being studied. After RNA isolation, the choice of profiling platform and data analysis is another consideration. While either microarray or RNA sequencing can be used to determine genome-wide transcriptomes, as mentioned earlier, they each have their advantages and disadvantages (thoroughly reviewed by Cox et al., 2015). Data analysis considerations include whether to identify differentially expressed genes or broad categories of dysregulated pathways in case–control studies and to ensure adequate statistical adjustment to account for multiple testing, i.e. false discovery correction. Technical notes and methods to visualize these data are further discussed in a recent review by Konwar et al. (2019).

Data validation

Another key aspect is to validate the findings from transcriptome analyses. Expression changes should ideally be confirmed at the RNA and protein levels by techniques, such as real-time qPCR, immunoblotting, enzyme-linked immunosorbent assays and immunohistochemistry. Furthermore, *in vitro* functional assays with primary explant cultures or isolated cells and *in vivo* animal models would provide deeper mechanistic insights into the role of identified genes.

Transcriptome studies of healthy placental development

Studies assessing healthy placentas (Table I) have three general aims: to investigate transcriptome changes across gestation, to characterize cell populations within the placenta or to determine the regulation and variability of gene expression across individual placentas.

Gestation-specific effects

Transcriptome datasets exist for each trimester of pregnancy, allowing identification of gestation-specific signatures (Table I: Gestation effects). Two microarray datasets contain placental expression profiles across all trimesters and serve as useful references of the temporal changes that occur during development (Mikheev et al., 2008; Soncin et al., 2018). Unsurprisingly, a common finding of first-trimester studies is an enrichment of highly expressed genes involved in cell proliferation and cell-cycle regulation (Mikheev et al., 2008; Sitras et al., 2012; Lim et al., 2017b; Soncin et al., 2018), which reflects rapid placental growth in early gestation. Interrogation of a large third-trimester microarray dataset of 157 placentas in conjunction with detailed histological analyses enabled markers of normal villous maturation to be identified, which was used to establish a method to calculate the molecular age in weeks of a given placenta, enabling a maturation measure to be assigned to placentas from pathological pregnancies (Leavey et al., 2017). However, the overall number of just under 300 placentas represented by these datasets is still relatively small, particularly for the first and second trimesters with data from only 73 and 21 placentas respectively, and expanding the number of samples profiled will enable elimination of spurious findings and further refinement of gestation-specific transcriptome signatures of placental development.

Cellular characterization and differentiation

The placenta comprises many different cell types. To improve resolution of gene expression to the cellular level, multiple studies have performed global profiling of isolated cells or primary cell cultures from the maternal–foetal interface (Table I: Cellular characterization and differentiation). However, an important caveat is that in addition to varying cell purity of the derived sample, differences may arise in the cellular response to the isolation and/or culture methods, which could become a source of bias and lead to data artefacts that are indistinguishable from naturally occurring *in vivo* differences. Moreover, aside from one study, datasets in this theme are derived from studies with fewer than 13 individual placentas each, with the majority having five or fewer. This is understandable, given the technical complexities and high time investment involved in isolating and culturing placental cells. However, such a limitation may lead to conclusions that may not fully reflect the natural diversity between individual placentas. Nonetheless, they can still serve as valuable baseline references for future studies in this area.

Trophoblast cells are unique to the placenta and therefore a major cell type specifically targeted for genome-wide transcript profiling. Cytotrophoblast cells are precursors of the extravillous trophoblast and syncytiotrophoblast. Extravillous trophoblast cells are responsible for maternal tissue invasion and placentation, while syncytiotrophoblast forms the maternal–foetal exchange barrier and acts as a major source of endocrine and paracrine factors for supporting pregnancy. However, common trophoblast isolation methods disrupt the multinucleated synctiotrophoblast layer, resulting in most studies focussing on just the cytotrophoblast and extravillous trophoblast cells. Extrapolation of their results to the understanding of syncytiotrophoblast function must, therefore, be made with extreme caution. Furthermore, one key finding is that cultured term placental trophoblast cells, as well as endothelial cells, have sex-specific expression patterns, with the male placental transcriptome enriched for pathways involved in the immune system and inflammatory response, which may partly explain the general observation of poorer outcomes for pregnancies with a male foetus (Cvitic et al., 2013). Hence, future studies should consider having a large enough sample size to stratify analyses by sex or be able to account for the possible influence of sex on the cell-specific gene expression profiles.

Recent studies have used single-cell RNA sequencing with microfluidics to characterize gene expression profiles of a variety of individual cells at the maternal–foetal interface. Although the first single-cell study only sequenced 87 cells from just two-term placentas (Pavlicev et al., 2017), it provided an important proof of concept for successfully applying this technology to interrogate the placental transcriptome.

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Table III Pregnancy exposures.

Year	Accession ID	Platform	Type	Tissue/cell	Sampling location	Total no.	Gestation	Purpose	Associated publications
Obesity									
2013	EBI ArrayExpress E-MTAB-4541	Affymetrix Human Gene 2.0 ST Array	Microarray	Tissue	Chorionic villi	10 –5 lean –5 obese	3rd trimester	Obese vs lean before pregnancy	Altmae *et al.* (2017)
2018	NCBI SRA PRJNA478464	Illumina NextSeq 500 -mean sequencing depth ~31M	RNA-seq	Tissue	Placenta biopsy (no details provided)	13 –6 lean –7 obese	3rd trimester	Obese vs lean before pregnancy	Sureshchandra *et al.* (2018)
2019	NCBI GEO GSE128381	Agilent-039494 SurePrint G3 Human GE v2 8 × 60K 039381	Microarray	Tissue	Chorionic villi	183 –108 lean –75 overweight or obese	3rd trimester	Across a continuum of maternal pre-pregnancy BMI including 41% overweight or obese	Cox *et al.* (2019)
	Not publically available	Illumina Genome Analyzer IIx –poly A+ selection –mean sequencing depth unavailable	RNA-seq	Tissue	Placenta biopsy (no details provided)	24 –12 lean –12 obese	3rd trimester	Obese vs lean before pregnancy	Saben *et al.* (2014a)
	Not publically available	Affymetrix HuGene ST 1.0 Array	Microarray	Tissue (laser microdissected)	Placenta biopsy (no details provided)	12 –4 lean –4 obese –4 obese GDM	3rd trimester	GDM vs obese non-diabetic vs lean controls	Bari *et al.* (2016)
Smoking									
2007	NCBI GEO GSE7434	Affymetrix Human Genome U133 Plus 2.0 Array	Microarray	Tissue	Placenta biopsy (no details provided)	10 –5 C –5 smokers	3rd trimester	Smoking vs non-smoking controls	Huuskonen *et al.* (2008)
2009	NCBI GEO GSE18044	Illumina humanRef-8 v2.0 Expression Beadchip	Microarray	Tissue	Chorionic villi	76 –64 C –12 smokers	3rd trimester	Smoking vs non-smoking controls	Bruchova *et al.* (2010)
2011	NCBI GEO GSE27272	Illumina HumanRef-8 V3.0 Expression Beadchip	Microarray	Tissue	Chorionic villi	54 –37 C –17 smokers	3rd trimester	Smoking vs non-smoking controls	Votavova *et al.* (2011)
2011	NCBI GEO GSE30032	Illumina HumanRef-8 V3.0 Expression Beadchip	Microarray	Tissue	Chorionic villi	57 –32 C –25 passive	3rd trimester	Passive smokers vs non-smoking controls	Votavova *et al.* (2012)

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Table III Continued

Year	Accession ID	Platform	Type	Tissue/cell	Sampling location	Total no.	Gestation	Purpose	Associated publications
Clinical trials									
2012	NCBI GEO GSE39290	Agilent-014850 Whole Human Genome Microarray 4 × 44K G4112F	Microarray	Tissue	Placenta biopsy (basal plate + chorionic plate + chorionic villi)	12 –6 low –6 high	3rd trimester	High vs low choline intake in third trimester	Jiang *et al.* (2013)
2014	NCBI GEO GSE53291	Affymetrix NuGO array (human) NuGO_Hs1a520180	Microarray	Tissue	Chorionic villi	16 –7 placebo –9 treated	3rd trimester	Omega-3 supplementation vs placebo	Sedlmeier *et al.* (2014)
2015	EBI ArrayExpress E-MTAB-6418	Illumina HumanHT-12 V4.0 Expression Beadchip	Microarray	Tissue	Placenta biopsy (basal plate + chorionic plate + chorionic villi)	108 –54 placebo –54 treated	3rd trimester	Obese women treated with metformin vs placebo	Chiswick *et al.* (2016)
IVF									
2018	NCBI GEO GSE122214	Affymetrix Human Genome U133 Plus 2.0 Array	Microarray	Tissue	Chorionic villi	8 –4 C –4 IVF	1st trimester	IVF vs controls	Zhao *et al.* (2019)
	Not publically available	Affymetrix GeneChip Human Gene 1.0 ST Array	Microarray	Tissue	Chorionic villi	20 –10 C –10 IVF	3rd trimester	IVF vs controls	Nelissen *et al.* (2014)
	Not publically available	Illumina –mean sequencing depth ~21M	RNA-seq	Tissue	Chorionic villi	141 –74 C –34 IVF –33 non-IVF	1st trimester	IVF or non-IVF fertility treated vs controls	Lee *et al.* (2019)
Antenatal depression									
2014	Available as supplementary data within journal article	Affymetrix GeneChip Human Gene 1.0 ST Array	Microarray	Tissue	Placenta biopsy (chorionic plate + chorionic villi)	20 –10 C –10 depressed –10 depressed + SSRI	3rd trimester	Depressed women with and without SSRI treatment vs controls	Olivier *et al.* (2014)

IVF, *in vitro* fertilisation; SSRI, selective serotonin reuptake inhibitor.

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Additionally, given the limitation of microfluidics in isolating large cells, the authors utilized laser microdissection to facilitate more accurate profiling of the large multi-nucleated syncytiotrophoblast (Pavlicev et al., 2017), in sharp contrast to subsequent studies that merely dissociated placental tissues and then reported cellular characterization of the syncytiotrophoblast. Although one of these studies acknowledged the shortcomings of the cellular dissociation approach that undoubtedly alters transcript profiles, and the possible under-representation of synctiotrophoblast profiling in the data (Suryawanshi et al., 2018), this consideration was neglected and ignored by the rest (Tsang et al., 2017; Liu et al., 2018; Vento-Tormo et al., 2018). Hence, the current available data are likely biased and not fully reflective of syncytiotrophoblast gene expression across gestation, and should be viewed and used with some caution. Given the important role the syncytiotrophoblast serves as the active cellular and regulatory barrier between mother and foetus, future studies should strive to better profile the synctiotrophoblast, and ensure isolation methods are carefully justified and weaknesses accounted for to allow proper interpretation of findings.

Another methodological factor to consider is the additional mechanical stress following tissue dissociation imposed by either a pre-enrichment of cells by magnetic bead separation (Liu et al., 2018) or pre-sorting of cells by fluorescence-activated cell sorting (Vento-Tormo et al., 2018), which may potentially modify the observed gene expression patterns. A first-trimester study without prior pre-selection did, however, demonstrate a good correlation (Pearson r value of 0.86) of the multi-cell transcriptome of an average villi assessed by single-cell RNA sequencing with that assessed by bulk tissue RNA sequencing, suggesting that overall, tissue dissociation and subsequent microfluidics techniques have only minor effects on the gene expression profiles for most dissociated cells (Suryawanshi et al., 2018). Thus, these latter single-cell sequencing studies can be considered to have collectively established for the first time, at the single-cell level, cell-specific gene expression profiles of the maternal–foetal interface throughout gestation, which serve as a potential reference to deconvolute placental cellular heterogeneity in future bulk tissue studies.

Gene expression variation and regulation

Another purpose of analysing the healthy placental transcriptome is to discover how gene expression is regulated and its variability across different regions of each placenta and between individuals (Table I: Gene expression variation and regulation). One study of third-trimester placentas estimated that while more than half of term placental gene variation was due to differences between individuals, a significant third of variation was attributable to intra-individual differences, compared with only <10% of variation due to ethnic background (Hughes et al., 2015). Foetal-placental sex is a major contributor to inter-individual variation, with sexual dimorphism predominantly arising from differential expression of genes on the sex chromosomes (Gonzalez et al., 2018). Some of the observed differences between individuals and between tissue biopsies of the same placenta likely also arise from cellular heterogeneity, as evidenced by a single-cell sequencing study showing different cellular proportions between individual samples biopsied from within the same placental region and from sample replicates obtained from the same placenta (Tsang et al., 2017). Furthermore, multi-regional sampling of the placenta and associated tissues, such as the decidua and umbilical cord, highlights distinct gene expression patterns associated with each sampling region (Sood et al., 2006; Kim et al., 2012). All of these underscore the importance of sampling region selection (Fig. 2) and having a sufficiently large sample size with multi-site sampling of the same region within each placenta to overcome variations, due to sample collection and intra-individual and inter-individual placental differences, to produce robust datasets reflective of the true 'experimental' group differences in question.

Additionally, there are clusters of genes that demonstrate relatively consistent placental expression between individuals and throughout pregnancy regardless of gestation, while others are trimester-specific and even show conserved expression patterns between humans and mice (Buckberry et al., 2017). These consistently expressed genes are likely key regulatory genes indispensable for normal overall placental function and for directing temporal-specific changes relating to the particular requisite functions of the placenta at each trimester.

Attempts to discover what underlies placental gene transcriptional regulation have explored genotype and methylation, which are DNA-based, in association with the transcriptome. Indeed, two large RNA sequencing studies comprising a total of 239 individual placentas with genotype data showed a consistent overlap of 381 expression quantitative trait loci (eQTLs), suggesting that the placental expression of genes in these loci are under stringent genetic control (Peng et al., 2017; Delahaye et al., 2018). Methylation is also associated with variation in placental gene expression. Dual profiling of the third-trimester placental transcriptome and methylome showed that DNA methylation accounted for a greater variance of birthweight than gene expression profiles at a single timepoint, and identified *MSX1* and *GRB10* methylation as potential master regulators in the transcriptional control of growth-related genes in the term placenta (Turan et al., 2012). Hence, these studies highlight the complexities of placental gene expression regulation which may drive the large variation of expression observed between and within individual placentas and subsequent birth outcomes.

Placental transcriptome studies of pregnancy complications

Improved understanding of the pathophysiology of pregnancy complications is a main driver for interrogating the placental transcriptome (Table II). Studies in this research theme have compared placentas from the normal and pathological states and are discussed taking into account the considerations of study design mentioned above.

Pre-eclampsia

Pre-eclampsia, a serious hypertensive disorder of pregnancy, is the most common pathology in which the placenta has been profiled, with 40 datasets produced from a total of 1192 placentas (44% affected). These datasets represent approximately a fifth of all placental transcriptome datasets (Table II:Pre-eclampsia). Given the nature of pre-eclampsia, difficulty in prediction of its onset and challenges with sampling placenta from ongoing pregnancies, most of the placentas profiled were collected in the third trimester at delivery, during the advanced stages of the disorder. Nevertheless, there is a single study of 12 samples collected from controls and women who subsequently developed

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Table IV *In vitro* placental cultures.

Year	Accession ID	Platform	Type	Model	Treatment	Source	Purpose	Associated publications
Trophoblast cultures								
2004	NCBI GEO GSE1302	Affymetrix Human Genome U95B Array, Affymetrix Human Genome U95C Array, Affymetrix Human Genome U95D Array, Affymetrix Human Genome U95E Array, Affymetrix Human Genome U95 Version 2 Array	Microarray	Primary cytotrophoblast culture	Peroxisome proliferator-activated receptor gamma ligand GW7845	Term placenta	Assess accuracy of microarray data	Mecham *et al.* (2004)
2005	NCBI GEO GSE2531	Affymetrix Human Genome U133A Array	Microarray	Cytrophoblast cell lines	None	JEG-3 and BeWo	Compare trophoblast cell lines	Burleigh *et al.* (2007)
2008	NCBI GEO GSE13475	Affymetrix Human Genome U133 Plus 2.0 Array	Microarray	Cytrophoblast cell lines	Transfected with STOX1 overexpression plasmid	JEG-3	Determine effect of STOX1 overexpression on trophoblast function	Rigourd *et al.* (2008)
2010	NCBI GEO GSE20510	Affymetrix Human Genome U133A Array	Microarray	Cytotrophoblast and extravillous trophoblast cell lines	None	SGHPL-5, HTR-8/SVneo, BeWo, JEG-3 and ACH-3P	Compare trophoblast cell lines	Bilban *et al.* (2010)
2011	EBI ArrayExpress E-MEXP-2800	Agilent Whole Human Genome Microarray 4 × 44K 014850 G4112F	Microarray	Cytotrophoblast cell line	Infected with *Coxiella burnetii*	BeWo	Determine pathways of *Coxiella burnetii* (Q fever) placental infection in trophoblast	Ben Amara *et al.* (2010)
2011	NCBI GEO GSE27909	Affymetrix Human Genome U133 Plus 2.0 Array	Microarray	Extravillous trophoblast cell line	Hoechst dye	HTR-8/SVneo	Compare side population (consists of stem and progenitor cells) and non-side trophoblast population	Takao *et al.* (2011)
2011	NCBI GEO GSE20404	Affymetrix Human Gene 1.0 ST Array	Microarray	Cytotrophoblast cell line	Heme oxygenase-1 silencing	BeWo	Assess effect of HO-1 silencing on trophoblast cell adhesion	Tauber *et al.* (2010)
2011	NCBI GEO GSE31679	Illumina HumanHT-12 V3.0 expression beadchip	Microarray	Extravillous trophoblast cell line	Cobalt chloride, interleukin-1-beta, tumour necrosis factor alpha	Swan-71	Assess effects of chemical hypoxia and pro-inflammatory cytokines on trophoblast function	Unpublished
2012	NCBI GEO GSE40182	Affymetrix Human Genome U133 Plus 2.0 Array	Microarray	Primary cytotrophoblast culture	Exposed to pre-eclampsia *in vivo*	3rd trimester placenta	Assess long-term effect of exposure to pre-eclampsia *in vivo* on trophoblast	Zhou *et al.* (2013)
2012	NCBI GEO GSE30330	Agilent Whole Human Genome Microarray 4 × 44K 014850 G4112F	Microarray	Cytotrophoblast cell line	Infected with *Coxiella burnetii*	JEG3	Determine pathways of *Coxiella burnetii* (Q fever) placental infection in trophoblast	Unpublished

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Table IV Continued

Year	Accession ID	Platform	Type	Model	Treatment	Source	Purpose	Associated publications
2012	NCBI GEO GSE41441	Agilent-012391 Whole Human Genome Oligo Microarray G4112A	Microarray	Cytotrophoblast cell line	Valproic acid	JEG-3	Determine adverse effects of valproic acid on trophoblast	Unpublished
2013	NCBI GEO GSE49922	Agilent-028004 SurePrint G3 Human GE 8 × 60K Microarray	Microarray	Primary cytotrophoblast culture	Irradiation	Term placenta	Determine irradiated trophoblast response	Kanter *et al.* (2014)
2013	NCBI GEO GSE41331	Illumina HumanHT-12 V4.0 Expression Beadchip	Microarray	Primary cytotrophoblast culture	Hypoxia	Term placenta	Determine hypoxic trophoblast response	Yuen et al. (2013)
2014	EBI ArrayExpress E-MTAB-429	Illumina HumanHT-12 v3.0 Expression BeadChip	Microarray	Cytotrophoblast and extravillous trophoblast primary culture and cell lines	None	First-trimester placenta, JAR and JEG-3	Compare trophoblast cell lines	Apps *et al.* (2011)
2014	NCBI GEO GSE56564	Agilent-028004 SurePrint G3 Human GE 8 × 60K Microarray	Microarray	Primary cytotrophoblast culture and extravillous trophoblast cell line	Transfected with plasmid for C19MC miRNA expression	Term placenta; HTR-8/SVneo	Determine effect of C19MC miRNA on trophoblast function	Xie *et al.* (2014)
2015	NCBI GEO GSE60432	Agilent-028004 SurePrint G3 Human GE 8 × 60K Microarray	Microarray	Primary cytotrophoblast culture	Hypoxia	Term placenta	Determine hypoxic trophoblast response	Unpublished
2016	NCBI GEO GSE79333	Stanford Functional Genomics Facility SHDZ	Microarray	Primary cytotrophoblast and syncytiotrophoblast culture	*In vitro* differentiation	Term placenta	Characterize *in vitro* cytotrophoblast differentiation	Rouault *et al.* (2016)
2016	NCBI GEO GSE73016	Illumina HiSeq 2500 -poly A+ selection -mean sequencing depth ~25M	RNA-seq	Primary cytrophoblast culture	Time course differentiation	Term placenta	Compare synctytiotrophoblast derived from placenta and human pluripotent stem cells	Yabe *et al.* (2016)
2017	NCBI GEO GSE98523	Applied Biosystems Human Genome Survey Microarray Version 2	Microarray	Cytotrophoblast cell line	*In vitro* differentiation with forskolin	BeWo	Characterize *in vitro* cytotrophoblast differentiation	Gauster *et al.* (2018)
2017	NCBI GEO GSE86171	Affymetrix Human Genome U133 Plus 2.0 Array	Microarray	Primary cytotrophoblast culture	*In vitro* differentiation with Matrigel	2nd trimester placenta	Characterize *in vitro* cytotrophoblast differentiation	Robinson *et al.* (2017)
2017	NCBI SRA PRJNA383955	Illumina HiSeq 2500 -mean sequencing depth ~16M	RNA-seq	Cytotrophoblast cell line	Dexamethasone	Not stated, obtained from cell bank	Determine trophoblast response to dexamethasone	Shang *et al.* (2018)
2018	NCBI SRA PRJNA397241	Illumina HiSeq 2500 -mean sequencing depth ~104M	RNA-seq	Primary cytotrophoblast culture and cell line	*In vitro* differentiation by time course or with forskolin	Term placenta and BeWo	Characterize *in vitro* cytotrophoblast differentiation	Azar *et al.* (2018)

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Table IV Continued

Year	Accession ID	Platform	Type	Model	Treatment	Source	Purpose	Associated publications
2018	NCBI GEO GSE65866	Illumina HumanHT-12 V4.0 Expression Beadchip	Microarray	Cytotrophoblast cell line	*ZNF554* silencing	BeWo	Determine role of ZNF554 in trophoblast function	Than *et al.* (2018)
2018	NCBI GEO GSE65940	Illumina HumanHT-12 V4.0 Expression Beadchip	Microarray	Extravillous trophoblast cell line	*ZNF554* silencing	HTR-8/SVneo	Determine role of ZNF554 in trophoblast function	Than *et al.* (2018)
2018	NCBI GEO GSE66304	Illumina HiSeq 2000 -poly A+ selection -mean sequencing depth ~57M	RNA-seq	Cytotrophoblast cell line	*PEG10* silencing	JEG-3	Determine role of PEG10 in trophoblast function	Unpublished
2018	NCBI GEO GSE118351	Affymetrix Human Gene Expression Array	Microarray	Primary cytotrophoblast culture	Time course differentiation	Term placenta	Characterize *in vitro* cytotrophoblast differentiation	Unpublished
2019	NCBI GEO GSE125778	Illumina Genome Analyzer IIx -poly A+ selection -mean sequencing depth ~17M	RNA-seq	Extravillous trophoblast cell line	Interferon-gamma	HTR-8/SVneo	Assess effect of interferon-gamma on trophoblast invasion	Verma *et al.* (2018)
2019	NCBI GEO GSE124586	Illumina HiSeq 2000 -poly A+ selection -mean sequencing depth ~33M	RNA-seq	Extravillous trophoblast cell line	Epidermal growth factor	HTR-8/SVneo	Assess effect of epidermal growth factor on trophoblast invasion	Unpublished
2019	NCBI GEO GSE127170	Affymetrix Human Gene 1.0 ST Array	Microarray	Cytotrophoblast cell line	*In vitro* differentiation with forskolin	BeWo and JEG-3	Identify genes associated with trophoblast fusion	Unpublished
	Not publically available	Affymetrix U95A array	Microarray	Primary cytotrophoblast culture	Hypoxia	Term placenta	Determine hypoxic trophoblast response	Roh *et al.* (2005)
	Not publically available	Illumina HiSeq 2500; Illumina Genome Analyzer IIx -poly A+ selection -mean sequencing depth ~24M	RNA-seq	Cytotrophoblast cell line	*In vitro* differentiation with forskolin	BeWo	Assess relationship of cell fusion transcriptome with methylome	Shankar *et al.* (2015)
	Not publically available	Affymetrix Human Gene 1.1 ST Array	Microarray	Primary cytotrophoblast culture	Insulin	1st trimester placenta	Investigate the effects of obesity and insulin on trophoblast	Lassance *et al.* (2015)
	Not publically available	Illumina HiSeq 2000 -poly A+ selection -mean sequencing depth ~35M	RNA-seq	Cytotrophoblast cell line	*In vitro* differentiation with forskolin	BeWo	Identify syncytialization-related genes in trophoblast	Zheng *et al.* (2016)

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Table IV Continued

Year	Accession ID	Platform	Type	Model	Treatment	Source	Purpose	Associated publications
Non-trophoblast cultures								
2006	NCBI GEO GSE5809	Affymetrix Human Genome U133 Plus 2.0 Array	Microarray	Primary decidualized stromal cell culture	Conditioned medium from primary first or second trimester trophoblast	Endometrial biopsy	Determine decidual response to trophoblast secretions/paracrine signals	Hess *et al.* (2007)
2010	NCBI GEO GSE21332	Illumina HumanWG-6 v3.0 Expression Beadchip	Microarray	Primary pericyte culture	None	Term placenta	Compare pericytes by tissue source	Maier *et al.* (2010)
2011	EBI ArrayExpress E-MEXP-3299	Applied Biosystems Human Genome Survey Microarray v2.0	Microarray	Primary placental endothelial cell culture	Foetal HDL	Term placenta	Identify apoE-HDL regulated genes in placental endothelium	Augsten *et al.* (2011)
2013	NCBI GEO GSE41946	Agilent-014850 Whole Human Genome Microarray 4 × 44K G4112F	Microarray	Primary decidual endothelial culture	None	1st trimester placenta	Compare immunoregulatory and pro-angiogenic functions of endothelial cells relative to tissue of origin	Agostinis *et al.* (2019)
2016	NCBI GEO GSE58220	Affymetrix Human Gene 2.0 ST Array	Microarray	Primary decidual stromal cell culture	Interleukin-1-beta	Term placenta	Determine decidual response to cytokine challenge	Ibrahim *et al.* (2016)
***In vitro* models of *in vivo* exposures**								
2012	NCBI GEO GSE36083	Affymetrix Human Genome U133 Plus 2.0 Array	Microarray	Primary explants	Antiphospholipid antibodies	1st trimester placenta	Determine trophoblast response to antiphospholipid antibodies	Pantham *et al.* (2012)
2017	NCBI GEO GSE104348	Illumina HiSeq 2500-mean sequencing depth ~65M	RNA-seq	Primary explants	Interferon-beta or interferon-lambda	2nd trimester placenta	Assess placental response to different interferons (in the context of Zika virus infection)	Yockey *et al.* (2018)
2018	NCBI GEO GSE113155	Agilent-039494 SurePrint G3 Human GE v2 8 × 60K Microarray 039381	Microarray	Primary explants	Infected with *Trypanosoma cruzi*	Term placenta	Assess placental response to *Trypanosoma cruzi* infection	Castillo *et al.* (2018)
	Not publically available	Illumina NextSeq 500 -poly A+ selection -mean sequencing depth unavailable	RNA-seq	Primary decidual and chorionic villus organoid cultures	Infected with Zika virus	1st trimester placenta	Assess decidual and chorion response to Zika virus infection	Weisblum *et al.* (2017)

HDL, high-density lipoprotein.

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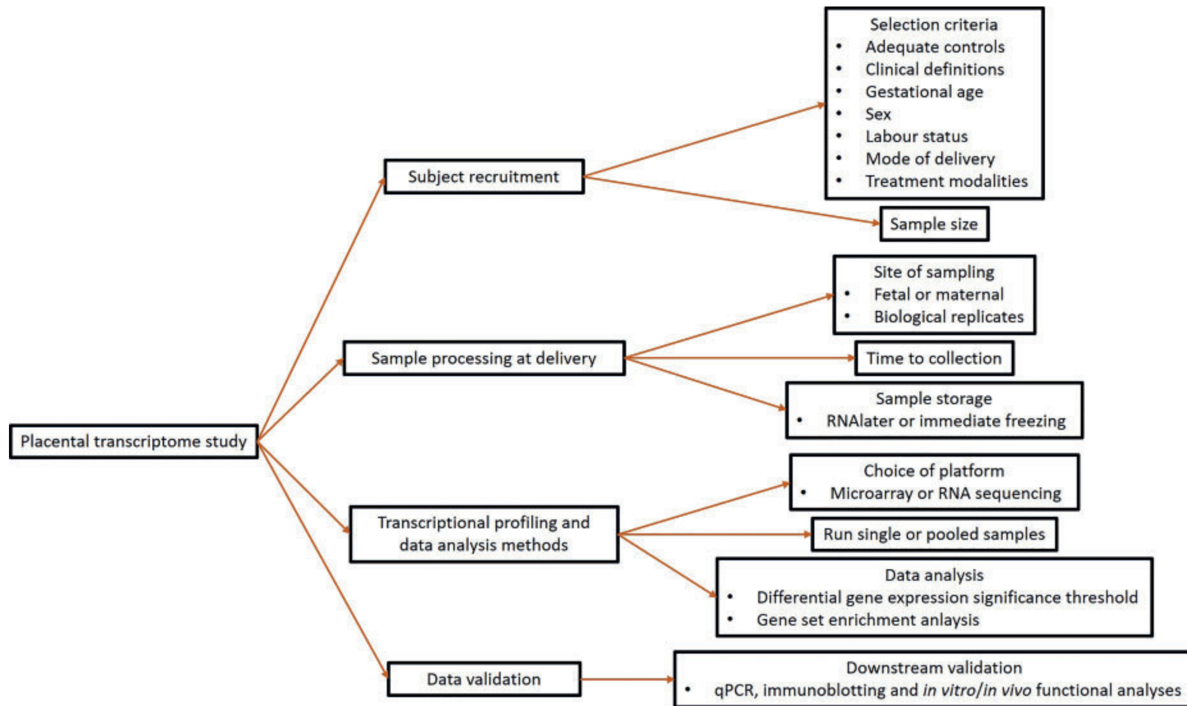

Figure 1. Key aspects to consider for placental transcriptome studies.

pre-eclampsia (Founds *et al.*, 2009). This study utilized surplus tissue obtained from first-trimester chorionic villus sampling and demonstrated placental dysregulation of genes involved in immune modulation, inflammation and cell motility months before the clinical manifestation of pre-eclampsia (Founds *et al.*, 2009), highlighting the early development of this insidious disease in the placenta. This dataset, while small, serves as a rare reference of the early placenta with known outcomes at delivery.

Expression profiling studies at the pre-eclamptic maternal–foetal interface frequently and consistently reveal dysregulated expression of genes involved in the oxidative stress and inflammatory pathways (Eide *et al.*, 2008; Loset *et al.*, 2011; Tsai *et al.*, 2011; Song *et al.*, 2013; Yong *et al.*, 2015; Tong *et al.*, 2018). Moreover, abnormal gene expression signatures of extravillous trophoblast cells, which was identified by the first single-cell RNA sequencing study of pre-eclamptic placenta, were also detectable in the maternal circulation in pre-eclampsia and may potentially serve as a non-invasive marker or 'liquid biopsy' of anomalous placental function in the future (Tsang *et al.*, 2017). Collectively, these studies highlight how pre-eclampsia affects multiple molecular pathways and functions of cells of both maternal and foetal origin at the placental interface, thereby underscoring the complexity of disease pathophysiology and the potential to develop some of these differentially expressed genes as biomarkers of pre-eclampsia.

Attempts have been made to delineate pre-eclampsia from other complications, such as gestational diabetes mellitus (GDM), intrauterine growth restriction (IUGR) and macrosomia (Sitras *et al.*, 2009a; Mayor-Lynn *et al.*, 2011; Nishizawa *et al.*, 2011; Guo *et al.*, 2013; Sober *et al.*, 2015; Lekva *et al.*, 2016; Gibbs *et al.*, 2019). Results of these studies are consistent with the notion that pre-eclampsia is heterogeneous, comprising of multiple molecular subtypes that distinctly cluster with other pregnancy pathologies (Guo *et al.*, 2013; Gibbs *et al.*, 2019), suggestive of a shared aetiology or pathophysiology involving the placenta (Nishizawa *et al.*, 2011; Sober *et al.*, 2015).

Molecular subtypes also seem to associate with gestation at onset of pre-eclampsia and placental histological findings, and efforts have been made to further characterize these subsets. Several studies sought to refine the sample population by either considering only early-onset pre-eclampsia developing before 34 weeks' gestation (Varkonyi *et al.*, 2011; Blair *et al.*, 2013; Than *et al.*, 2018), only late-onset pre-eclampsia developing from 34 weeks' gestation (Sober *et al.*, 2015; Lekva *et al.*, 2016) or both (Nishizawa *et al.*, 2007; Sitras *et al.*, 2009b; Junus *et al.*, 2012; Liang *et al.*, 2016; Tong *et al.*, 2018). A major issue in considering gestational age in placental studies is what construes an appropriate control. Of the 34 studies including preterm pre-eclampsia cases, about 21% used only preterm controls, while around 44% used only term controls, with the remainder including both preterm and term controls. Utilizing preterm controls in pre-eclampsia studies may actually confound study findings, given that preterm controls are frequently derived from those with premature rupture of membranes or preterm labour, which are also pregnancy pathologies and not an ideal reference of normal human pregnancy (Cox *et al.*, 2015). Conversely, it could be argued that the most severe pre-eclamptic cases are usually delivered preterm and should be compared with similarly preterm but non-pre-eclamptic cases since term gestation brings in another dimension that is unrelated to the pathology of pre-eclampsia and observed differences may be due purely to the effect of gestation rather than pre-eclampsia.

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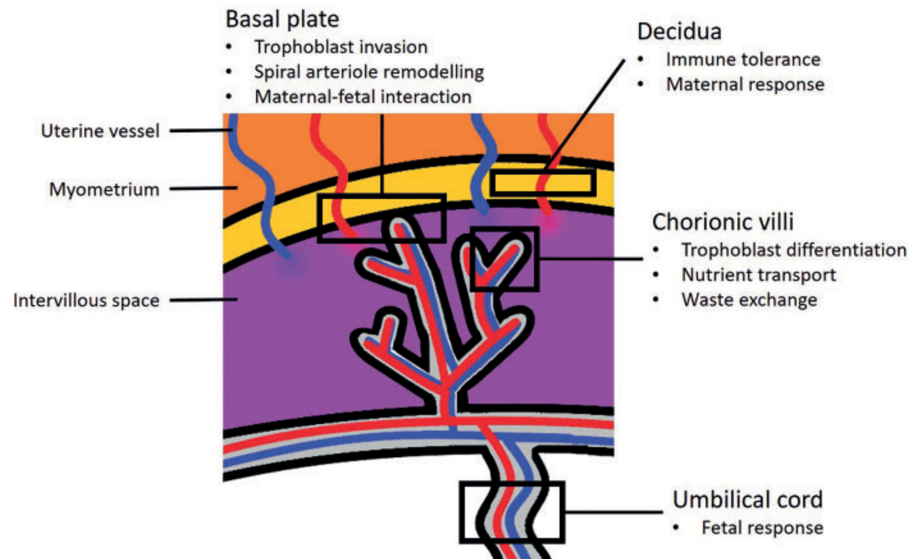

Figure 2. Placental regions commonly sampled for transcriptome analyses.

Hence, there remains no clear consensus within the field about the most optimal control for pre-eclamptic cases requiring preterm delivery and readers should carefully consider the interpretation of study findings whichever control is used.

Intrauterine growth restriction/small for gestational age

IUGR is the failure of a foetus to reach its full genetic growth potential *in utero*. Clinically, IUGR is often diagnosed with ultrasound findings of a small for gestational age (SGA) baby below the 10th centile, associated with abnormal uteroplacental blood flow (Kingdom *et al.*, 2018). This review considers 17 datasets representing a total of 721 placentas of which 26% were either from SGA- or IUGR-affected pregnancies (Table II: IUGR/SGA). Most placental transcriptome studies utilized only the criterion of SGA (McCarthy *et al.*, 2007; Sabri *et al.*, 2014; Sober *et al.*, 2015; Deyssenroth *et al.*, 2017; Verheecke *et al.*, 2018; Gibbs *et al.*, 2019), while some studies excluded those who may be healthy and constitutionally small, by including an additional criterion of a small abdominal circumference below the fifth centile (Guo *et al.*, 2013; Madeleneau *et al.*, 2015) or ultrasound findings of abnormal uteroplacental blood flow indicative of placental insufficiency (Roh *et al.*, 2005; Sitras *et al.*, 2009a; Struwe *et al.*, 2010; Nishizawa *et al.*, 2011; Dunk *et al.*, 2012; Majewska *et al.*, 2019). However, while some of these IUGR cases may be explained by maternal smoking, pre-eclampsia or chemotherapy during pregnancy (Sitras *et al.*, 2009a; Dunk *et al.*, 2012; Verheecke *et al.*, 2018), a considerable number of cases have no specific identifiable underlying cause and are termed idiopathic (Nishizawa *et al.*, 2011). Hence, a common and clear research definition of IUGR is lacking within the placenta community. Moreover, as discussed earlier, gestational age is another potential confounder, with 8 out of 11 studies that included preterm IUGR cases utilizing term controls.

Nevertheless, a degree of consistency exists between these various studies, hinting at shared placental pathways involved in the pathophysiology of IUGR regardless of gestation. Dysregulated expression of genes involved in the processes of placental growth signalling, mitochondrial respiration and a hypoxic response was observed in multiple IUGR studies (Roh *et al.*, 2005; McCarthy *et al.*, 2007; Struwe *et al.*, 2010; Guo *et al.*, 2013; Sabri *et al.*, 2014; Madeleneau *et al.*, 2015; Deyssenroth *et al.*, 2017; Verheecke *et al.*, 2018). Several studies also demonstrated a substantial overlap between pre-eclampsia and normotensive growth restriction, encompassing genes involved in the molecular processes of placental angiogenesis and immune regulation (Sitras *et al.*, 2009a; Nishizawa *et al.*, 2011; Dunk *et al.*, 2012; Guo *et al.*, 2013; Sober *et al.*, 2015; Gibbs *et al.*, 2019; Majewska *et al.*, 2019). Additional research to increase understanding of placental function in growth-compromised pregnancies could improve diagnosis and management of cases.

Macrosomia/large for gestational age

Conversely, some infants are macrosomic or large for gestational age (LGA). At present, four studies comprising 263 placentas (28% affected) have examined the placental transcriptome in relation to excessive intrauterine growth (Table II: Macrosomia/LGA). As with growth restriction, little consensus exists on defining excessive growth. Some studies selected cases based on an absolute birthweight cut-off of >4 kg (Song *et al.*, 2018), while others utilize birthweight percentiles customized for sex and gestational age at a cut-off of over 90th percentile (Sabri *et al.*, 2014; Sober *et al.*, 2015; Deyssenroth *et al.*, 2017); both of which do not account for the possibility of including normal constitutionally large babies. One study demonstrated that placentas of LGA babies had similar expression patterns to that of late-onset pre-eclampsia, which is often not associated with growth restriction, alluding to some common disturbances in placental function

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(Sober *et al.*, 2015). Growing evidence also indicates that besides short-term morbidities of birth trauma, excessive intrauterine growth is also associated with poorer long-term cardiometabolic outcomes in offspring (Szostak-Wegierek, 2014). Thus, being large at birth should not be regarded as benign and more resources should be dedicated to understanding the possible placental mechanisms involved to prevent the potential intrauterine programming of adverse health outcomes manifesting in later life.

Gestational diabetes mellitus

Rates of GDM are rising worldwide. Follow-up studies suggest intrauterine exposure to maternal hyperglycaemia leads to poorer health outcomes in offspring (Binder *et al.*, 2015). A total of 10 studies have profiled 282 placentas (44% affected) with respect to GDM (Table II: GDM). Again, criteria used to define GDM is varied. The World Health Organisation changed the criteria for diagnosis quite substantially between its 1999 and 2013 guidelines, while the American College of Obstetricians and Gynaecologists, UK National Institute for Health and Care Excellence and other countries continue using different diagnostic criteria (Meek, 2017). Nonetheless, most studies demonstrate that immune and inflammatory genes are among the most consistently dysregulated in placentas from GDM pregnancies (Radaelli *et al.*, 2003; Enquobahrie *et al.*, 2009; Zhao *et al.*, 2011; Binder *et al.*, 2015). In contrast, two transcriptome studies found few or no significant placental expression changes between GDM and controls (Sober *et al.*, 2015; Lekva *et al.*, 2016). However, these two studies had other pathological groups including pre-eclampsia, SGA or LGA, and such as the statistical power may have been insufficient to identify differentially expressed genes or clusters associated with each condition, although the overall sample size was large (Sober *et al.*, 2015; Lekva *et al.*, 2016).

Studies have also considered other forms of diabetes in pregnancy, such as pre-existing type I and type II diabetes (Radaelli *et al.*, 2009; Alexander *et al.*, 2018) or tried to account for differences in maternal obesity, which is more common in diabetic groups compared with controls (Bari *et al.*, 2016). However, as the numbers of each diabetic type or BMI group are small, more studies are needed to confirm if the identified differences are due to diabetes or obesity. Another issue is that of selective reporting. For example, in a genome-wide transcriptome study of type I diabetes and GDM cases and controls, the authors chose to report only pre-selected genes involved in glucose and lipid metabolism based on fold changes without correcting for multiple testing (Radaelli *et al.*, 2009), which is a biased approach and some results may turn out to be chance findings. Further studies are also needed to resolve the transcript differences associated with GDM management (diet-control, metformin or insulin treatment) or quality of glycaemic control, functionally explore the biological significance of identified placental gene expression alterations, and expand knowledge into the underlying pathophysiology of GDM and its possible implications for offspring health.

Antenatal infections and inflammation

Infections during pregnancy not only affect the mother but can also impact the foetus via the placenta. Three studies (total n = 53 placentas, 40% affected) have examined the transcriptome of placentas exposed to malaria, *Trypanosoma cruzi* and infections leading to preterm birth (Table II: Antenatal infections and inflammation). Expectedly, all affected placentas, regardless of infection type, show dramatic upregulation of genes involved in the immune and inflammatory response (Muehlenbachs *et al.*, 2007; Ackerman *et al.*, 2016; Juiz *et al.*, 2018). Better understanding of the functional significance of these transcriptomic alterations may lead to the identification of biomarkers or therapeutic targets for improved clinical management of infections during pregnancy, and reduce infection-induced preterm birth and adverse developmental programming.

Placental inflammation may also occur in the absence of an infection. At present, two studies (total n = 31 placentas, 52% affected) have examined cases of placental inflammation without infection (Table II: Antenatal infections and inflammations). Placentas with villitis of unknown aetiology show transcript profiles distinct from that of chorioamnionitis caused by an infection, suggesting that the pathology may arise from maternal–foetal histoincompatibility (Kim *et al.*, 2009). Comparison of the chronically inflamed placenta with controls also suggests a key role of T cells in mediating maternal immune tolerance of foetal antigens, which may underlie chronic placental inflammation (Raman *et al.*, 2015). Nevertheless, given the small number of studies with low sample sizes, larger studies in this area are clearly needed to confirm the findings of these past studies. It would also be interesting to explore the transcriptome profiles of autoimmune conditions, such as systemic lupus erythematosus, and those pregnancies exposed to immunosuppressive therapy (e.g. post-organ transplant), as these conditions are associated with increased risk of adverse pregnancy outcomes.

Labour

The exact mechanisms of parturition remain elusive. Presently, five datasets have examined 89 placentas and decidua in relation to labour onset (Table II: Labour), of which four involved preterm labour (27% affected). The inflammatory response is consistently identified as the most dysregulated process at the preterm labour placental interface (Chim *et al.*, 2012; Bukowski *et al.*, 2017; Rinaldi *et al.*, 2017). Aberrant expression of genes involved in extracellular matrix remodelling is also implicated in preterm labour, which may in turn be affected by abnormal expression of miRNAs (Mayor-Lynn *et al.*, 2011; Chim *et al.*, 2012). Further refinement and validation of these labour-associated molecular factors in larger studies will enhance understanding of the normal parturition process and may lead to development of novel biomarkers to predict the onset of labour in pregnant women and interventions for either prevention of preterm labour or obstetrically indicated induction of labour.

Recurrent miscarriage

Recurrent miscarriage (RM) is the repeated loss of pregnancy in the early stages and affects around 1 in 50 couples (Rull *et al.*, 2013). The precise cause(s) of RM is unknown for many couples, but five small studies (n = 50 placentas, 42% affected) have investigated the placental transcriptome to uncover the potential factors involved in unexplained RM (Table II: RM). It is nonetheless difficult to distinguish between transcriptomic changes that lead to the miscarriage as opposed to those that change as a result of the miscarriage process. Moreover, given that products of conception may remain *in utero* for days after pregnancy failure or embryo/foetal demise, placental RNA quality may

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be compromised by the time of collection and be another study confounder. Controls in such studies are those of elective termination of pregnancies with no known anomalies. However, the use of such controls is based on an underlying assumption that these pregnancies would have ended well without any complications, which is impossible to verify. A proposed alternative control could be first-trimester placentas collected from women who had previous successful term pregnancies, but happen to experience their first miscarriage, which presumably would likely be of a conceptus-originated aetiology rather than a parental-originated aetiology that is more likely in cases of RM.

Despite questions over suitability of controls and very small sample sizes, current studies still provide an initial insight into potential mechanisms. For instance, a microarray study identified tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) as highly expressed in RM placentas, which was detectable in the circulation of women both at the point of miscarriage and also prior to miscarriage (i.e. in women who subsequently had a miscarriage following prospective blood sampling), as compared with controls (Rull *et al.*, 2013). Increased circulating TRAIL was verified in an independent study, which also demonstrated adverse effects of high TRAIL concentrations on trophoblast function *in vitro* (Agostinis *et al.*, 2012), indicating TRAIL as a potential biomarker and determinant of pregnancy failure in early gestation. Other studies show association of RM with transcription factors, such as E2F and YY1, non-coding RNAs and DNA methylation (Sober *et al.*, 2016; Tian *et al.*, 2016; Huang *et al.*, 2018; Yu *et al.*, 2018), which are yet to be validated in larger datasets.

Chromosomal abnormalities

Profiling placentas containing chromosomal abnormalities provide a unique opportunity to study *in vivo* effects of genetic aberrations and inform on the pathogenesis of complications that occur as the pregnancy progresses. Just two studies have examined 38 placentas (58% affected) so far (Table II: Chromosomal abnormalities). Interrogating the trisomy 21 placental transcriptome revealed differential expression of genes associated with neurodevelopment, cancer and diabetes (Lim *et al.*, 2017a), which may explain the disease risks of trisomy 21 individuals. Other transcriptomic investigation of placentas of either trisomy 13, 18 or 21 showed that several highly expressed genes were located on the respective trisomic chromosome, which is reflective of gene dosage (Bianco *et al.*, 2016). However, most of the up-regulated genes were surprisingly not located on the trisomic chromosome, suggesting knock-on effects genome-wide (Bianco *et al.*, 2016). These studies suggest that the observed phenotypes of aneuploidy, including pregnancy loss and IUGR, may arise from the collective effects of gene dosage and complex downstream genome-wide dysregulation of genes in the placenta (Bianco *et al.*, 2016).

Intrahepatic cholestasis of pregnancy

Intrahepatic cholestasis of pregnancy (IHCP), also known as obstetric cholestasis, is associated with preterm delivery and stillbirths (Bicocca *et al.*, 2018). The aetiology of the observed maternal pruritus and liver impairment may be associated with an enhanced response to increased oestrogen production in pregnancy resulting in abnormal hepatobiliary transport (Bicocca *et al.*, 2018). At present, only one study of 30 placentas (67% affected) has examined the genome-wide placental transcript profile (Table II: Intrahepatic cholestasis of pregnancy). This study showed dysregulation of genes involved in vascular endothelial growth factor, G-protein-coupled receptor and immune-related signalling, with a greater dysregulation correlating with disease severity, thus, implicating abnormal placental angiogenesis and immune response in the pathophysiology of IHCP (Du *et al.*, 2014). As with the other complications of pregnancy previously discussed, severe cases tended to deliver preterm and gestational age may be a confounder influencing the results observed since the study used term controls. Further studies are, therefore, needed to extend the knowledge of placental involvement in this complication of pregnancy.

Placental transcriptome studies of exposures during pregnancy

Many maternal sociodemographic factors, lifestyle and environmental exposures have been linked with pregnancy complications and offspring health adversity. A better understanding of how these different exposures affect the placenta will provide a greater insight into the pathophysiology and biological pathways leading to complications and abnormal programming of offspring health. As such, studies in this research theme examined placentas from pregnancies with different exposures from assisted reproduction and various clinical trial interventions to pre-existing maternal conditions (Table II).

Obesity

Alarmingly, a growing number of women are entering pregnancy in an obese state worldwide. Being obese markedly increases the risks of pregnancy complications, such as pre-eclampsia, GDM and preterm delivery (Sureshchandra *et al.*, 2018). Transcript profiling of placentas from obese women may uncover the underlying basis of their heightened risk of pregnancy complications and the molecular mechanisms involved in programming offspring health. Five placental transcriptome studies ($n = 242$, 44% affected) have considered maternal obesity (Table III: Obesity). Two studies similarly found enrichment of differentially expressed genes involved in angiogenesis, lipid metabolism and the immune/inflammatory response (Saben *et al.*, 2014a; Altmae *et al.*, 2017). A different study identified perturbed placental nutrient transport as another consequence of exposure to the maternal obesity milieu (Sureshchandra *et al.*, 2018), which could alter foetal growth and postnatal health trajectories. Indeed, a large study of 183 placentas examining maternal pre-pregnancy BMI as a continuous variable demonstrated that gene clusters enriched for maternal immune dysregulation were positively associated with maternal BMI and negatively associated with low birth weight, providing evidence of a molecular basis to the relationship between the two (Cox *et al.*, 2019). Therefore, the placenta exposed to maternal obesity is characterized by immune dysregulation, which can have widespread effects on placental function and foetal growth and development.

Smoking

Tobacco smoke is an external environmental exposure that is detrimental to pregnancy. Global profiling of smoke-exposed placentas in four studies ($n = 197$, 30% affected, Table II: Smoking) showed harmful and dysregulating effects of tobacco smoke on different aspects of

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placental growth and metabolism (Huuskonen *et al.*, 2008; Bruchova *et al.*, 2010; Votavova *et al.*, 2011; Votavova *et al.*, 2012). Comparison of smoke-induced transcriptomic changes in placenta by active or passive smoking showed a substantial overlap between both groups compared with the non-smoking group in biological processes, such as lipid metabolism, oxidative stress and blood coagulation (Votavova *et al.*, 2012), suggesting that these common molecular placental mechanisms are involved in transmitting the harm of smoking to the growing foetus be it active or passive. As such, these placental pathways could be potential intervention targets to modify the pregnancy outcomes of those exposed to any type of tobacco smoke during gestation.

Clinical trials

Various nutritional or drug interventions are being explored in clinical trials to improve pregnancy outcomes. While treatments may show promising results *in vitro* on placental cell cultures and *in vivo* in animal models, many have not shown the desired effect upon testing in most clinical trials. Transcript profiling of placentas from women treated as part of a clinical trial during pregnancy may thus provide valuable insights into the underlying molecular mechanisms affected, inter-individual variability in effects and possible explanation for trial findings. We identified three studies that analysed a total of 136 placentas from clinical trials (Table II: Clinical trials). A study conducted on placentas collected from women supplemented with a low or high dose of choline from the start of the third trimester, with the intention of improving placental vascular function and reducing the risk of developing pre-eclampsia, showed widespread effects on the placental transcriptome, particularly on processes involved in vascular regulation (Jiang *et al.*, 2013). A promising finding was significantly reduced expression of the pre-eclampsia-associated *FLT1* gene, which can induce systemic vascular dysfunction at high protein concentrations, thus providing a molecular basis for the utility of choline supplementation during pregnancy (Jiang *et al.*, 2013). Omega-3 fatty acid supplementation altered placental expression of genes involved in cell-cycle regulation in a sexually dimorphic manner with greater changes occurring in pregnancies with female foetuses, which correlated with offspring birthweight and birthweight centiles (Sedlmeier *et al.*, 2014). This study highlights the placental response to omega-3 supplementation and the potential mechanisms involved in modulating foetal growth and postnatal development (Sedlmeier *et al.*, 2014). A third study examined placentas collected from obese women who were treated with metformin or a placebo (Chiswick *et al.*, 2016), with the aim of determining if there were any changes in genes regulating foetal growth or metabolism. However, while the transcriptome dataset is publically available alongside complementary methylome data, the study findings remain unpublished. Nevertheless, this dataset serves as a valuable resource to understand the effects of metformin on the placenta and acts as a possible reference for studies involving metformin in treatment of GDM.

In vitro fertilization

With the global rise of ART, more pregnancies are now being conceived by IVF, which is associated with poorer pregnancy outcomes (Nelissen *et al.*, 2014). Three studies have examined the IVF placental transcriptome in the first and third trimesters (n = 169 placentas, 28% exposed, Table III: *In vitro* fertilization). To determine which differentially expressed genes are related more specifically to IVF, the largest study of 141 first-trimester chorionic villus samples included a non-IVF ART group alongside spontaneous conceptions for comparison and identified *CACNA1I*, which codes for a calcium channel subunit, as one such gene (Lee *et al.*, 2019). Further comparison between just the IVF and non-IVF ART groups showed differential expression of *SLC18A2*, *CCL21*, *FXYD2*, *PAEP* and *DNER*, which supports the notion that IVF also has distinct effects on the placenta compared with other types of ART (Lee *et al.*, 2019). However, as ART are used primarily by couples who struggle to conceive naturally, discovered alterations may be due to the underlying parental factors contributing to subfertility rather than a result of ART used. Since infertility causes are so varied, such as being due to structural defects of the reproductive tract, ovulatory dysfunction, endometriosis, childhood cancer chemotherapy or unexplained maternal or paternal factors, stratifying by causes of infertility may help discriminate the unique gene signatures for infertility as compared with those that are consequential of ART in future studies.

Antenatal depression

Antenatal maternal mental health is of rising importance as cumulative evidence suggests a potent impact on pregnancy and childhood outcomes. Currently, only one study (n = 20 placentas, 50% affected, Table III: Antenatal depression) has examined the effects of maternal depression and antidepressant treatment on the placental transcriptome (Olivier *et al.*, 2014). Most differentially expressed genes compared with controls showed limited overlap between the untreated and medically treated depression (Olivier *et al.*, 2014). This suggests that not only does depression itself affect the placental transcriptome, but that depression and antidepressants have largely independent effects on the placenta and that those treated with antidepressants should be evaluated separately in future studies.

Transcriptome studies of *in vitro* placental cultures

The key advantage of culturing *in vitro* explants or isolated cells from the placenta is that we can determine the precise effects of altering a single factor in well-controlled experimental conditions, without having to contend with other inter-individual variability in inter-placental comparisons. Transcript profiling of cultured placental explants, primary cells and cell lines have thus also contributed to increased understanding of placental function, with many studies profiling the placental response to various agents and treatments including hypoxia, irradiation, growth factors, cytokines and infectious agents (Table III). Such *in vitro* models have limitations including issues with cell purity of isolated primary cells, loss of 3D cytoarchitecture and absence of cell–cell interaction in single-cell type cultures. Although placental explant and organoid cultures may overcome some of these limitations, culture conditions may not fully reflect *in vivo* conditions and could lead to spurious findings as a result of altered responses to the exposure of interest. Hence, transcriptome findings of *in vitro* models should be interpreted with some caution and further verified in *ex vivo* studies.

Trophoblast cultures

Most *in vitro* studies utilize primary trophoblast cultures from term placenta or extended trophoblast cell lines. Given the common use of

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immortalized cell lines in placental research, widely-used trophoblast-like cell lines were profiled to ascertain their genome-wide phenotype and how representative they were of primary trophoblast (Burleigh *et al.*, 2007; Bilban *et al.*, 2010; Apps *et al.*, 2011; Takao *et al.*, 2011). These studies found little overlap in the profiles between primary cells and cell lines, and recommended caution in use of cell lines in placental research (Burleigh *et al.*, 2007; Bilban *et al.*, 2010; Apps *et al.*, 2011). Another reason for genome-wide profiling of cultured trophoblast is to characterize the differentiation process from cytotrophoblast to syncytiotrophoblast (Shankar *et al.*, 2015; Rouault *et al.*, 2016; Yabe *et al.*, 2016; Zheng *et al.*, 2016; Robinson *et al.*, 2017; Azar *et al.*, 2018; Gauster *et al.*, 2018). Pairing genome-wide transcript profiling with targeted gene manipulation using small RNA or plasmid technologies allows gene regulatory effects to be determined alongside consequential effects on trophoblast cell function (Rigourd *et al.*, 2008; Tauber *et al.*, 2010; Xie *et al.*, 2014; Than *et al.*, 2018), despite the potential limitations in methodology discussed earlier.

Non-trophoblast cultures

Additionally, several studies have examined non-trophoblast cell types in culture. For example, to expand knowledge on the genetic regulation of placental vascularity, Augsten *et al.* (2011) performed a microarray on primary term placental endothelial cells treated with high-density lipoprotein to assess how foetal lipoprotein, which contains a considerably higher proportion of apoE than that of adults, alters placental vessel function. Another microarray study identified genes involved in the immunoregulatory and pro-angiogenic function of first-trimester decidual endothelial cells relative to another endothelial cell type from skin (Agostinis *et al.*, 2019), providing an insight into the unique role of these maternal endothelial cells in modulating immune tolerance of the foetus at the interface. Transcriptome studies of non-trophoblastic cells remain few, and if conducted and interpreted with the caution discussed previously, further investigations utilizing cultures of these cell types may potentially enhance understanding of the complex processes occurring in pregnancy.

In vitro models of *in vivo* exposures

Placental-derived cultures are also used to mimic *in vivo* exposures. For instance, several datasets reflect the response profile of placental explants, trophoblast cell lines, primary decidual and chorion organoid cultures exposed to infectious agents – *Coxiella burnetii*, *Trypanosoma cruzi* and Zika virus (Ben Amara *et al.*, 2010; Weisblum *et al.*, 2017; Castillo *et al.*, 2018), which are further informed by related studies that examine the effects of immunomodulatory cytokines on placental function (Ibrahim *et al.*, 2016; Verma *et al.*, 2018; Yockey *et al.*, 2018). One study characterized the molecular signatures of the response to insulin in trophoblast cells cultured from first-trimester placentas of lean and obese women, revealing that prior exposure to obesity blunted trophoblast sensitivity to insulin (Lassance *et al.*, 2015). Notwithstanding the technical limitations that may impact transcriptome findings, placental-derived cultures can add another dimension in expanding knowledge of placental function, which may not be fully apparent from study of tissues and immediately isolated cells.

Knowledge gaps and future directions

Addressing placental heterogeneity

Cellular heterogeneity of the human placenta is likely a major contributing factor to inconsistent transcriptome findings between studies. With the advent of single-cell transcriptomics, it may be possible to deconvolute the placental tissue transcriptome more readily and account for differences in tissue sampling in the near future. Deconvolution may also highlight differences in placental cell composition due to the underlying pathology. Single-cell human placental transcriptome profiles across all trimesters are now available and serve as a basis to develop algorithms for deconvolutions (Table I). However, sample sizes in these studies are relatively small between two and ten placentas and with the current technical limitations requiring cell dissociation, available datasets may include artefactual changes and not fully capture the transcriptome of all placental cell types, particularly the large multi-nucleated syncytiotrophoblast.

Meta-analysis of current data and ease of data access

Meta-analysis of past studies enhances statistical power, which may highlight novel molecular pathways or strengthen the evidence for previously identified genes. Indeed, multiple meta-analyses have been performed for pre-eclampsia (Kleinrouweler *et al.*, 2013; Moslehi *et al.*, 2013; Vaiman *et al.*, 2013; van Uitert *et al.*, 2015; Vaiman and Miralles, 2016; Brew *et al.*, 2016) and preterm birth (Eidem *et al.*, 2015; Paquette *et al.*, 2018), as well as for investigating sexual dimorphism of the placenta (Buckberry *et al.*, 2014) and understanding trophoblast differentiation in the context of hydatidiform moles (Desterke *et al.*, 2018). Nevertheless, lack of data access can hamper the ability to perform powerful meta-analyses. For example, of the 10 transcript profiling studies performed for GDM, only data from three studies are publically available, representing less than a third of the profiled placentas. Efforts are ongoing to make placental data more accessible. For instance, the newly developed Placenta Atlas Tool centralized database simplifies the search for relevant placental transcriptome datasets and allows some basic analysis to be performed within the site (Ilekis *et al.*, 2019), providing a useful starting point for researchers. Consistent and clear reporting of experimental details, such as specific microarray platforms utilized and poly A+ selection for mRNA enrichment in RNA sequencing studies, and of key clinical information to inform on disease subtypes and severity are also critical in enabling researchers to design proper integrative meta-analysis studies.

Studies on non-coding RNA

Traditionally, much focus was on protein-coding mRNA transcripts that result in functional changes. However, growing evidence implicate possible roles for non-coding RNA (e.g. long non-coding RNA, miRNA, circular RNA) in the placenta (Cox *et al.*, 2015). Differential placental expression of non-coding RNAs has been investigated in pre-eclampsia (Gunel *et al.*, 2017; Hu *et al.*, 2018a; Lykoudi *et al.*, 2018; Zhou *et al.*, 2018), GDM (Li *et al.*, 2015; Wang *et al.*, 2019b), IUGR or SGA pregnancies (Wen *et al.*, 2017; Ostling *et al.*, 2019) and early pregnancy loss (Hosseini *et al.*, 2018). The use of RNA sequencing

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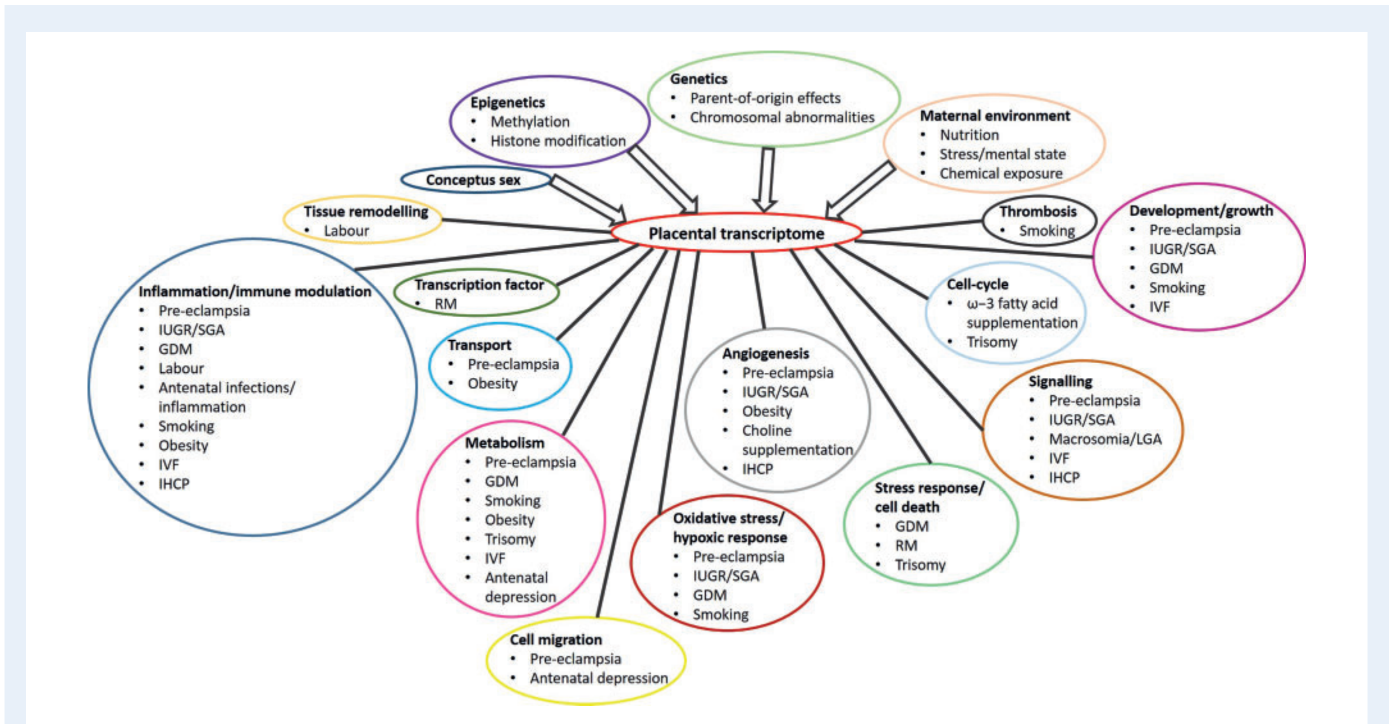

Figure 3. Factors that influence the placental transcriptome and the associations of altered placental molecular pathways with pregnancy complications or exposures. Dynamic transcriptional regulation of the placental interface throughout gestation is multi-factorial (arrows). Differential regulation of specific molecular pathways identified in multiple placental transcriptome studies may highlight the potential underlying causal mechanisms involved in pregnancy complications or represent the placental mechanisms affected by pregnancy exposures (connecting lines). GDM, gestational diabetes mellitus; IHCP, intrahepatic cholestasis of pregnancy; IUGR/SGA, intrauterine growth restriction/small for gestational age; LGA, large for gestational age; RM, recurrent miscarriage.

technologies to further characterize these non-coding RNAs provides a tantalizing approach to identify and develop new biomarkers and therapeutic targets for pregnancy complications. As such, researchers may want to consider the different RNA extraction methods available to enable capture of all placental RNA species, both coding and non-coding, for analysis in future studies.

Further studies on other issues in pregnancy

There is a paucity of genome-wide transcriptome studies in many aspects of pregnancy (Supplementary Table SII). The pre-eclamptic placenta is disproportionately profiled as compared with other common pathologies of pregnancy including preterm labour, IUGR, GDM and stillbirth (Table II). Although an estimated 2.6 million stillbirths occur annually worldwide (Blencowe *et al.*, 2016), of which ~40% are unexplained (Reinebrant *et al.*, 2018), no study has yet profiled placentas from this devastating pregnancy complication, although such studies could yield useful insights as to why a foetus dies *in utero*, especially in cases of unexplained stillbirth. Transcript profiling of abnormal placental development, such as placenta praevia, placenta accreta and molar pregnancy could also highlight the potential causative factors behind their pathogenesis (Desterke *et al.*, 2018), possibly enabling the discovery of new approaches to treat or prevent the recurrence of these pathologies in future pregnancies.

Additionally, even with much ongoing research effort to minimize infectious diseases, pregnant women, being relatively immunosuppressed, remain at great risk of infections, such as malaria (Dellicour *et al.*, 2010) and have shown increased susceptibility to recent global health emergencies, such as the swine flu pandemic and Ebola outbreak (Kourtis *et al.*, 2014; Silasi *et al.*, 2015). We propose that placental transcriptome studies be used to improve understanding of how maternal infections affect the placenta, so as to identify the mechanistic pathways that can be targeted to reduce the transmission of harm to the growing foetus.

Furthermore, given the increasingly recognized importance of the maternal nutritional, mental and emotional states, the rise in women exposed to harmful environmental and chemical exposures during their pregnancies and the profound impacts these can have on the pregnancy and the future health of the child (Hoirisch-Clapauch *et al.*, 2015; Lewis *et al.*, 2015; Unger *et al.*, 2016; Chen *et al.*, 2018; Henschke, 2019; Varshavsky *et al.*, 2019), their effects on the placenta are all deserving of further investigation, so as to increase ways of promoting benefits of some lifestyles while minimizing adversity. Pre-existing medical conditions (e.g. autoimmune and endocrine diseases, thrombophilia) are strongly associated with an aberrant hormonal, metabolic and inflammatory milieu that is detrimental to placentation, and thus, such pregnancies are predisposed to significantly higher rates of complications with poorer neonatal outcomes (Ali *et al.*, 2016; Vannuccini *et al.*, 2016; Meakin *et al.*, 2017; De Leo and Pearce, 2018; De Carolis *et al.*, 2019; Mitriuc *et al.*, 2019; Stepien and Huttner,

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2019). Placental transcriptome analysis could thus reveal how such conditions heighten a woman's susceptibility to obstetric complications, which may lead to new treatments to prevent defective placental function and improve pregnancy outcomes in affected women.

Pregnancy-specific factors can also have profound consequences on pregnancy outcomes. Given major societal changes, more women are using ART to conceive and/or entering pregnancy at an older age, both of which are associated with placental dysfunction and more obstetric problems including IUGR and stillbirth (Nelissen *et al.*, 2014; Lean *et al.*, 2017). Placental profiling may help reveal whether higher rates of obstetric complications observed are due to underlying subfertility or ART as suggested by animal studies (de Waal *et al.*, 2015), and enable appropriate strategies to be developed for mitigating harms.

Frequently excluded from transcriptome studies, profiling placentas from multiple pregnancies may also demonstrate the mechanisms involved in the inherently elevated risk of obstetric complications (Witteveen *et al.*, 2016), which could be targeted to improve outcomes for the mother and her children. Moreover, further studies of twin placental transcriptomes with disconcordant intrauterine growth, whereby the healthy twin can serve as a well-matched control (Roh *et al.*, 2005; Wen *et al.*, 2017), may help elucidate novel mechanisms of foetal growth that can be capitalized upon to improve IUGR outcomes.

Linkages with other 'omics' and long-term outcomes

Integrating placental transcriptome data with other datasets including other 'omics' and longitudinal data will enhance knowledge into healthy placental development and disease mechanisms. A study comparing the pre-eclamptic placental transcriptome to the blood transcriptome of cardiovascular disease identified significant overlap between the two, and provided novel insights into possible shared relationships between pregnancy complications and subsequent health in the mother or child postnatally (Sitras *et al.*, 2015). Placental transcript profiling in birth cohorts with comprehensive longitudinal follow-up of the children may also potentially uncover new placental programming mechanisms that can influence extrauterine life in the longer term. Indeed, previously identified placental eQTLs were predictive of birthweight and subsequent childhood obesity in a cohort study, highlighting the role of placental gene expression in modulating postnatal outcomes, and such genes could serve as potential molecular targets for interventions (Peng *et al.*, 2018). Besides profiling more placentas from additional birth cohorts, it is of great interest to examine currently available birth cohort-related placental transcriptome datasets for any possible associations with childhood outcomes (Binder *et al.*, 2015; Cox *et al.*, 2019). In doing so, we may be able to develop a catalogue of placental biomarkers predictive of future health, which could be used to identify offspring at high risk of subsequent poor health. Thus, the placenta may serve as a unique window into the future extrauterine life of the offspring and provide an opportunity to intervene and change the health trajectories of those exposed to an adverse intrauterine environment.

Conclusion

Placental transcript profiling presents enormous potential to enhance understanding of healthy placental development and function, highlight the possible underlying causal and consequential mechanisms of pregnancy complications (Fig. 3), and predict and improve the health outcomes of mothers and offspring from compromised pregnancies. Challenges in obtaining sufficient numbers of quality samples with clear clinical characteristics will need to be overcome to drive the field forward. Current data may also be capitalized upon by performing meta-analyses to increase statistical power, although interpretation of findings will need to carefully account for limitations, such as inconsistent clinical criteria between studies and gestational age matching of cases and controls. Furthermore, additional resources should be dedicated to analyse placentas from the understudied areas, which will enable the dynamic complexities of the placental transcriptome to be more fully appreciated.

Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

Authors' roles

H.E.J.Y. contributed to the study design, performed the literature searches and wrote and edited the manuscript. S.Y.C. conceived the study and provided critical revision of the manuscript for intellectual content.

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Conflict of interest

H.E.J.Y. has no conflict of interest to declare. S.Y.C. is part of the EPIGEN academic consortium that has received research funding from Nestec.

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