METHODS AND SYSTEMS FOR DETERMINING A PREGNANCY-RELATED STATE OF A SUBJECT

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Patent Application No. 62/805,515, filed February 14, 2019, U.S. Patent Application No. 62/890,248, filed August 22, 2019, and U.S. Patent Application No. 62/926,786, filed October 28, 2019, each of which is entirely incorporated by reference herein.

BACKGROUND

[0002] Every year, about 15 million pre-term births are reported globally. Pre-term birth may affect as many as about 10% of pregnancies, of which the majority are spontaneous pre-term births. Currently, there may be no meaningful, clinically actionable diagnostic screenings or tests available for many pregnancy-related complications such as pre-term birth. However, pregnancy-related complications such as pre-term birth are a leading cause of neonatal death and of complications later in life. Further, such pregnancy-related complications can cause negative health effects on maternal health. Thus, to make pregnancy as safe as possible, there exists a need for rapid, accurate methods for identifying and monitoring pregnancy-related states that are non-invasive and cost-effective, toward improving maternal and fetal health.

SUMMARY

[0002a] The present disclosure provides a use of a drug in the manufacture of a medicament for treating a pregnant subject for a pre-term birth due to a pregnancy-related hypertensive disorder, wherein: (a) a cell-free blood sample is to be obtained from said pregnant subject; (b) nucleic acid molecules obtained or derived from said cell-free blood sample are to be assayed to determine at least one ribonucleic acid (RNA) level of at least one pregnancy-associated genomic locus, wherein said at least one pregnancy-associated genomic locus is differentially expressed in a first population of subjects with pre-term birth due to said pregnancy-related hypertensive disorder as compared to a second population of subjects without pre-term birth due to said pregnancy-related hypertensive disorder, wherein said assaying comprises selectively enriching said nucleic acid molecules for said at least one pregnancy-associated genomic locus, wherein said selectively enriching comprises use of nucleic acids having sequence complementarity with a nucleic acid sequence of said at least one pregnancy-associated genomic locus, wherein said at least one pregnancy-associated genomic locus is selected from the group consisting of genes listed in Table 5, genes listed in Table 6, genes listed in Table 8, RAB27B, RGS18, CLCN3, B3GNT2, COL24A1, CXCL8, and PTGS2; (c) said at least one RNA level of said at least one pregnancy-associated genomic locus determined in (b) is to be computer processed (i) against at least one reference RNA level of said at least one pregnancy-associated genomic locus or (ii) using a trained machine learning algorithm; wherein (d) said pregnant subject is determined to have or be at risk of having pre-term birth due to said pregnancy-related hypertensive disorder based at

least in part on said computer processing in (c); and wherein (e) the drug is to be administered to said pregnant subject to treat said pre-term birth due to said pregnancy-related hypertensive disorder, based on said determination in (d).

[0003] The present disclosure provides methods, systems, and kits for identifying or monitoring pregnancy-related states by processing cell-free biological samples obtained from or derived from subjects. Cell-free biological samples (e.g., plasma samples) obtained from subjects may be analyzed to identify the pregnancy-related state (which may include, e.g., measuring a presence, absence, or relative assessment of the pregnancy-related state). Such subjects may include subjects with one or more pregnancy-related states and subjects without pregnancy-related states. Pregnancy-related states may include, for example, pre-term birth, full-term birth, gestational age, due date (e.g., due date for an unborn baby or fetus of a subject), onset of labor, pregnancy-related hypertensive disorders (e.g., preeclampsia), eclampsia, gestational diabetes, a congenital disorder of a fetus of the subject, ectopic pregnancy, spontaneous abortion, stillbirth, post-partum complications (e.g., post-partum depression, hemorrhage or excessive bleeding, pulmonary embolism, cardiomyopathy, diabetes, anemia, and hypertensive disorders), hyperemesis gravidarum (morning sickness), hemorrhage or excessive bleeding during delivery, premature rupture of membrane, premature rupture of membrane in pre-term birth, placenta previa (placenta covering the cervix), intrauterine/fetal growth restriction, macrosomia (large fetus for gestational age), neonatal conditions (e.g., anemia, apnea, bradycardia and other heart defects, bronchopulmonary dysplasia or chronic lung disease, diabetes, gastroschisis, hydrocephaly, hyperbilirubinemia, hypocalcemia, hypoglycemia, intraventricular hemorrhage, jaundice, necrotizing enterocolitis, patent ductus arteriosis, periventricular leukomalacia, persistent pulmonary hypertension, polycythemia, respiratory distress syndrome, retinopathy of prematurity, and transient tachypnea), and fetal development stages or states (e.g., normal fetal organ function or development, and abnormal fetal organ function or development).

[0004] In an example, the present disclosure provides a method for identifying a presence or susceptibility of a pregnancy-related state of a subject, comprising assaying transcripts and/or metabolites in a cell-free biological sample derived from the subject to detect a set of biomarkers, and analyzing the set of biomarkers with a trained algorithm to determine the presence or susceptibility of the pregnancy-related state. In some examples, the method comprises assaying the transcripts in the cell-free biological sample derived from the subject to detect the set of biomarkers. In some examples, the transcripts are assayed with nucleic acid sequencing. In some examples, the method comprises assaying the metabolites in the cell-free biological sample derived from the subject to detect the set of biomarkers. In some examples, the metabolites are assayed with a metabolomics assay.

CLAIMS

WHAT IS CLAIMED IS:

1. Use of a drug in the manufacture of a medicament for treating a pregnant subject for a pre-term birth due to a pregnancy-related hypertensive disorder, wherein:

(a) a cell-free blood sample is to be obtained from said pregnant subject;

(b) nucleic acid molecules obtained or derived from said cell-free blood sample are to be assayed to determine at least one ribonucleic acid (RNA) level of at least one pregnancy-associated genomic locus, wherein said at least one pregnancy-associated genomic locus is differentially expressed in a first population of subjects with pre-term birth due to said pregnancy-related hypertensive disorder as compared to a second population of subjects without pre-term birth due to said pregnancy-related hypertensive disorder, wherein said assaying comprises selectively enriching said nucleic acid molecules for said at least one pregnancy-associated genomic locus, wherein said selectively enriching comprises use of nucleic acids having sequence complementarity with a nucleic acid sequence of said at least one pregnancy-associated genomic locus, wherein said at least one pregnancy-associated genomic locus is selected from the group consisting of genes listed in Table 5, genes listed in Table 6, genes listed in Table 8, RAB27B, RGS18, CLCN3, B3GNT2, COL24A1, CXCL8, and PTGS2;

(c) said at least one RNA level of said at least one pregnancy-associated genomic locus determined in (b) is to be computer processed (i) against at least one reference RNA level of said at least one pregnancy-associated genomic locus or (ii) using a trained machine learning algorithm; wherein

(d) said pregnant subject is determined to have or be at risk of having pre-term birth due to said pregnancy-related hypertensive disorder based at least in part on said computer processing in (c); and wherein

(e) the drug is to be administered to said pregnant subject to treat said pre-term birth due to said pregnancy-related hypertensive disorder, based on said determination in (d).

2. The use of claim 1, wherein ribonucleic acid (RNA) molecules derived from said cell-free blood sample are to be further reverse transcribed to produce complementary deoxyribonucleic acid (cDNA) molecules; and said cDNA molecules or derivatives thereof

are to be assayed to determine said at least one RNA level of said at least one pregnancy-associated genomic locus.

3. The use of claim 1, wherein said assaying comprises use of nucleic acid sequencing.

4. The use of claim 1, wherein said pregnancy-related hypertensive disorder is selected from the group consisting of preeclampsia and eclampsia.

5. The use of claim 1, wherein said cell-free blood sample comprises a plasma sample.

6. The use of claim 1, wherein said pregnant subject is asymptomatic for said pregnancy-related hypertensive disorder.

7. The use of claim 1, wherein said computer processing in (c) comprises using said trained machine learning algorithm.

8. The use of claim 7, wherein said trained machine learning algorithm is selected from the group consisting of a linear regression, a logistic regression, an analysis of variance (ANOVA) model, a deep learning algorithm, a support vector machine (SVM), a neural network, a Random Forest, and a combination thereof.

9. The use of claim 1, wherein said pregnant subject is to be further monitored for said pre-term birth due to said pregnancy-related hypertensive disorder at least in part by assessing said pre-term birth due to said pregnancy-related hypertensive disorder of said pregnant subject at a plurality of time points, wherein said assessing is based at least in part on determining whether said pregnant subject has or is at risk of having said pre-term birth due to said pregnancy-related hypertensive disorder at each of said plurality of time points.

10. The use of claim 9, wherein a difference in said assessing of said pre-term birth due to said pregnancy-related hypertensive disorder of said pregnant subject among said plurality of time points is indicative of one or more clinical indications selected from the group consisting of: (i) a diagnosis of said pre-term birth due to said pregnancy-related hypertensive disorder

of said pregnant subject, (ii) a prognosis of said pre-term birth due to said pregnancy-related hypertensive disorder of said pregnant subject, and (iii) an efficacy or non-efficacy of a therapeutic intervention for treating said pre-term birth due to said pregnancy-related hypertensive disorder of said pregnant subject.

11. The use of claim 4, wherein said pregnancy-related hypertensive disorder comprises said preeclampsia.

12. The use of claim 1, wherein said drug is selected from the group consisting of a hydroxyprogesterone caproate, a vaginal progesterone, a natural progesterone IVR product, a prostaglandin F2 alpha receptor antagonist, or a beta2-adrenergic receptor agonist.

13. The use of claim 4, wherein said pregnancy-related hypertensive disorder comprises said eclampsia.

14. The use of claim 7, wherein said trained machine learning algorithm is trained using a training dataset comprising: a first set of pregnant subjects with said pre-term birth due to said pregnancy-related hypertensive disorder, and a second set of pregnant subjects without said pre-term birth due to said pregnancy-related hypertensive disorder.

15. The use of claim 8, wherein said trained machine learning algorithm comprises said linear regression.

16. The use of claim 8, wherein said trained machine learning algorithm comprises said ANOVA model.

17. The use of claim 1, wherein said assaying comprises use of array hybridization.

18. The use of claim 1, wherein said assaying comprises use of polymerase chain reaction (PCR).

19. The use of claim 1, wherein said selectively enriching further comprises amplifying at least a portion of said nucleic acid molecules.

20. The use of claim 1, wherein said pregnant subject is to be further determined to have or be at risk of having said pre-term birth due to said pregnancy-related hypertensive disorder with a clinical sensitivity or clinical specificity of at least about 70%.

21. The use of claim 1, wherein said nucleic acids are primers or probes having sequence complementarity with said nucleic acid sequence of said at least one pregnancy-associated genomic locus.

22. The use of claim 21, wherein said nucleic acids are said probes having sequence complementarity with said nucleic acid sequence of said at least one pregnancy-associated genomic locus.