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 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 said pregnancy-related hypertensive disorder as compared to a second population of subjects without 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; (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 ~~an elevated~~ risk of having said pregnancy-related hypertensive disorder based at

CLAIMS

WHAT IS CLAIMED IS:

1. Use of a drug in the manufacture of a medicament for treating a pregnant subject for 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 said pregnancy-related hypertensive disorder as compared to a second population of subjects without 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;

(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 ~~an elevated~~ risk of having 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 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 pregnancy-related hypertensive disorder at least in part by assessing 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 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 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 pregnancy-related hypertensive disorder of said pregnant subject, (ii) a prognosis of said pregnancy-related hypertensive disorder of said pregnant subject, and (iii) an efficacy or non-efficacy of a therapeutic intervention for treating 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 corticosteroid, an antibiotic, a tocolytic drug, a calcium channel blocker, a cyclo-oxygenase inhibitor, an oxytocin antagonist, a betamimetic drug, magnesium sulfate, magnesium chloride, and magnesium oxide~~ 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 12, wherein said drug is said corticosteroid.~~

~~14. The use of claim 12, wherein said drug is said tocolytic drug.~~

~~15. The use of claim 12, wherein said drug is said magnesium sulfate.~~

13~~16~~. The use of claim 1, wherein delivery of a fetus of said pregnant subject is to be performed.

~~17. The use of claim 11, wherein said at least one pregnancy-associated genomic locus is differentially expressed by subjects with preeclampsia as compared to subjects without preeclampsia, wherein said at least one pregnancy-associated genomic locus comprises a member selected from the group consisting of PAPPA2, FABP1, GPSM2, CRH, and HP.~~

~~18. The use of claim 17, wherein said at least one pregnancy-associated genomic locus comprises three or more members selected from the group consisting of PAPPA2, FABP1, GPSM2, CRH, and HP.~~

14~~19~~. The use of claim 4, wherein said pregnancy-related hypertensive disorder comprises said eclampsia.

15~~20~~. 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 pregnancy-related hypertensive disorder, and a second set of pregnant subjects without said pregnancy-related hypertensive disorder.

1621. The use of claim 8, wherein said trained machine learning algorithm comprises said linear regression.

1722. The use of claim 8, wherein said trained machine learning algorithm comprises said ANOVA model.

1823. The use of claim 1, wherein said assaying comprises use of array hybridization.

1924. The use of claim 1, wherein said assaying comprises use of polymerase chain reaction (PCR).

2025. The use of claim 1, wherein said selectively enriching further comprises amplifying at least a portion of said nucleic acid molecules.

2126. The use of claim 1, wherein said pregnant subject is to be further determined to have said pregnancy-related hypertensive disorder with a clinical sensitivity or clinical specificity of at least about 70%.

2227. 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.

2328. The use of claim 227, wherein said nucleic acids are said probes having sequence complementarity with said nucleic acid sequence of said at least one pregnancy-associated genomic locus.