based on a certain ratio of sFLt-1 and PlGF imminent preeclampsia at the day of patient presentation could be ruled out (Stepan 2010, Z Geburtsh Neonatol 214: 234-238).

However, a reliable assay for ruling-out preeclampsia within a certain time period in an apparently healthy pregnant female is not yet available but nevertheless highly desired.

The technical problem underlying the present disclosure can be seen as the provision of means and methods for complying with the aforementioned needs. The technical problem is solved by the embodiments characterized in the claims and herein below.

The present disclosure~~, in a first aspect,~~ relates to a method for diagnosing whether a pregnant subject is not at risk for preeclampsia (i.e. ruling out preeclampsia) within a short window of time comprising:

a) determining the amount of at least one angiogenesis biomarker selected from the group consisting of sFlt-1, Endoglin and PlGF in a sample of said subject; and

b) comparing the amount with a reference, whereby a subject being not at risk for developing preeclampsia within a short period of time is diagnosed if the amount is identical or decreased compared to the reference in the cases of sFlt-1 and Endoglin and identical or increased in the case of PlGF, wherein said reference allows for making the diagnosis with a negative predictive value of at least about 98%.

The method of the present disclosure, preferably, is an ex vivo method. Moreover, it may comprise steps in addition to those explicitly mentioned above. For example, further steps may relate to sample pre-treatments or evaluation of the results obtained by the method. The method may be carried out manually or assisted by automation. Preferably, step (a), and/or (b) may in total or in part be assisted by automation, e.g., by a suitable robotic and sensory equipment for the determination in step (a), a computer-implemented calculation algorithm on a data processing device and/or comparison and/or diagnosis algorithm on a data processing device in step (b).

The present disclosure, in a second aspect, relates to a method for diagnosing whether a pregnant subject is not at risk for preeclampsia within a period ~~short window~~ of time of less than 4 weeks comprising:

a) determining the amounts of the biomarkers (i) sFlt-1 and P1GF or (ii) Endoglin and PlGF in a sample of said subject;

b) calculating a ratio from said amounts of (i) sFlt-1 and P1GF or (ii) Endoglin and PlGF determined in the sample in step a); and

c) comparing the value of the ratio with a reference value, whereby a subject being not at risk for developing preeclampsia within the~~a short~~ period of time is diagnosed if the value of the ratio is identical or decreased compared to the reference value, wherein said reference allows for making the diagnosis with a negative predictive value of at least about 98%%, and wherein said reference value is about 46 or less.

The present disclosure, in a third aspect, relates to use of at least one of the biomarkers sFlt-1, Endoglin and PlGF or at least one detection agent therefor which specifically bind thereto in a sample obtained from a pregnant subject for diagnosing whether said subject is not at risk for developing preeclampsia within a ~~short~~ period of time of less than 4 weeks, wherein said diagnosing is performed according to the method as defined herein.

The present disclosure, in a fourth aspect, relates to a device adapted for diagnosing whether a pregnant subject is not at risk for developing preeclampsia within a ~~short~~ period of time of less than 4 weeks by carrying out the method as defined herein comprising:

a) an analyzing unit comprising at least one detection agent which specifically binds to at least one angiogenesis biomarker selected from the group consisting of: sFlt-1, Endoglin and PlGF, said unit being adapted for determining the amount of sFlt-1, Endoglin and/or PlGF in a sample of a pregnant subject; and

b) an evaluation unit comprising a data processor having implemented an algorithm for comparing the amount with a reference, whereby a subject being not at risk for developing preeclampsia within a ~~short~~ period of time is diagnosed if the amount is identical or decreased compared to the reference in the cases of sFlt-1 and Endoglin and identical or increased in the case of PlGF, wherein said reference allows for making the diagnosis with a negative predictive value of at least about 98%, and wherein said reference value is about 46 or less,

wherein said analysing unit comprises detection agents for determining the amounts of the biomarkers(i) sFlt-1 and P1GF or (ii) Endoglin and PlGF in

the sample of said subject and wherein said algorithm implemented in the evaluation unit calculates a ratio of the amount of (i) sFlt1 and P1GF or (ii) Endoglin and PlGF and compares the value of ratio of the amount of (i) sFlt1 and P1GF or (ii) Endoglin and PlGF with a reference value, whereby a subject being not at risk for developing preeclampsia within the period of time is diagnosed if the value of the ratio is identical or decreased compared to the reference value.

~~The present disclosure, in a fifth aspect, relates to a kit adapted for carrying out the method as defined herein comprising at least one detection agent for determining the amount of an angiogenesis biomarker selected from the group consisting of: sFlt-1, Endoglin and PlGF, as well as instructions for carrying out the said method.~~

The term "preeclampsia" as used herein refers to a medical condition which is characterized by hypertension and proteinuria. Preeclampsia occurs in pregnant female

Claims

~~1. A method for diagnosing whether a pregnant subject is not at risk for preeclampsia within a short window of time comprising:~~

~~a) determining the amount of at least one angiogenesis biomarker selected from the group consisting of sFlt-1, Endoglin and PlGF in a sample of said subject; and~~

~~b) comparing the amount with a reference, whereby a subject being not at risk for developing preeclampsia within a short period of time is diagnosed if the amount is identical or decreased compared to the reference in the cases of sFlt-1 and Endoglin and identical or increased in the case of PlGF, wherein said reference allows for making the diagnosis with a negative predictive value of at least about 98%.~~

~~2~~1. A method for diagnosing whether a pregnant subject is not at risk for preeclampsia within a ~~short window~~ period of time of less than 4 weeks comprising:

a) determining the amounts of the biomarkers (i) sFlt-1 and P1GF or (ii) Endoglin and PlGF in a sample of said subject;

b) calculating a ratio from said amounts of (i) sFlt-1 and P1GF or (ii) Endoglin and PlGF determined in the sample in step a); and

c) comparing the value of the ratio with a reference value, whereby a subject being not at risk for developing preeclampsia within the ~~a short~~ period of time is diagnosed if the value of the ratio is identical or decreased compared to the reference value, wherein said reference allows for making the diagnosis with a negative predictive value of at least about 98%, and wherein said reference value is about 46 or less.

~~3~~2. The method of claim ~~2~~1, wherein said reference value is ~~about 46 or less, preferably, is~~ about 33.

~~4~~3. The method of claim ~~2~~1 ~~or 3~~, wherein said reference value is about 38 or less, preferably is about 38.

~~5~~4. The method of any one of claims 1 to ~~4~~3, wherein said ~~short~~ period of time is a time period from about 1 to about 2 weeks.

~~6~~5. The method of any one of claims 1 to ~~5~~4, wherein said pregnant subject is between about week 20 and about week 40 of gestation.

~~7~~6. The method of any one of claims 1 to ~~6~~5, wherein said sample is a blood, plasma, serum or urine sample.

~~8~~7. The method of any one of claims 1 to ~~7~~6, wherein said method further comprises recommending a patient management measure based on the diagnosis.

~~9~~8. The method of claim ~~8~~7, wherein said patient management measure (i) is selected from the group of the following measures if the subject is not diagnosed as being not at risk for developing preeclampsia: close monitoring, hospitalization, administration of blood pressure reducing agents and life style recommendations, and (ii) is ambulant monitoring if the subject is diagnosed as being not at risk for developing preeclampsia.

~~10~~9. Use of at least one of the biomarkers sFlt-1, Endoglin and PlGF or at least one detection agent therefor which specifically bind thereto in a sample obtained from a pregnant subject for diagnosing whether said subject is not at risk for developing preeclampsia within a ~~short~~ period of time of less than 4 weeks, wherein said diagnosing is performed according to the method of any one of claims 1 to 8.

~~11~~10. The method of any one of claims 1 to ~~9~~8 or the use of claim ~~10~~9, wherein said subject has been identified to be at risk for developing preeclampsia, eclampsia and/or HELLP syndrome based on abnormal Doppler ultrasonography results.

~~12~~11. A device adapted for diagnosing whether a pregnant subject is not at risk for developing preeclampsia within a ~~short~~ period of time of less than 4 weeks by carrying out the method of any one of claims 1 to ~~9~~8 or ~~11~~10 comprising:

a) an analyzing unit comprising at least one detection agent which specifically binds to at least one angiogenesis biomarker selected from the group consisting of: sFlt-1, Endoglin and PlGF, said unit being adapted for determining the amount of sFlt-1, Endoglin and/or PlGF in a sample of a pregnant subject; and

b) an evaluation unit comprising a data processor having implemented an algorithm for comparing the amount with a reference, whereby a subject being not at risk for developing preeclampsia within a ~~short~~ period of time is diagnosed if the amount is identical or decreased compared to the reference

in the cases of sFlt-1 and Endoglin and identical or increased in the case of PlGF, wherein said reference allows for making the diagnosis with a negative predictive value of at least about 98%, and wherein said reference value is about 46 or less, wherein said analysing unit comprises detection agents for determining the amounts of the biomarkers(i) sFlt-1 and P1GF or (ii) Endoglin and PlGF in the sample of said subject and wherein said algorithm implemented in the evaluation unit calculates a ratio of the amount of (i) sFlt1 and P1GF or (ii) Endoglin and PlGF and compares the value of ratio of the amount of (i) sFlt1 and P1GF or (ii) Endoglin and PlGF with a reference value, whereby a subject being not at risk for developing preeclampsia within the period of time is diagnosed if the value of the ratio is identical or decreased compared to the reference value.

~~13. The device of claim 12, wherein said analysing unit comprises detection agents for determining the amounts of the biomarkers(i) sFlt-1 and P1GF or (ii) Endoglin and PlGF in the sample of said subject and wherein said algorithm implemented in the evaluation unit compares the value of ratio of the amount of (i) sFlt1 and P1GF or (ii) Endoglin and PlGF with a reference value, whereby a subject being not at risk for developing preeclampsia within a short period of time is diagnosed if the value of the ratio is identical or decreased compared to the reference value.~~

~~14. The device of claim 12 or 13, wherein said algorithm implemented in the evaluation unit further calculates a ratio of the amount of (i) sFlt1 and P1GF or (ii) Endoglin and PlGF.~~

~~15. A kit adapted for carrying out the method of any one of claims 1 to 9 or 11 comprising at least one detection agent for determining the amount of an angiogenesis biomarker selected from the group consisting of: sFlt-1, Endoglin and PlGF, as well as instructions for carrying out the said method.~~

~~16. The kit of claim 15, wherein said kit comprises a detection agent for determining the amount of sFlt1 and/or Endoglin and a detection agent for determining the amount of PlGF in a sample of a pregnant subject.~~