intervening therapies when complications arise that require a direct therapeutic efficacy.

Consequently, there is a need to find a treatment that can manage PPH by effectively and reliably inducing myometrical contractions.

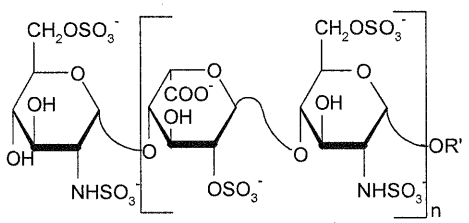
Summary

The present disclosure relates to the treatment or prevention of postpartum haemorrhage (PPH), whereby a chemically modified heparin or heparan sulfate with an antifactor IIa activity of less than 10 IU/mg and an antifactor Xa activity of less than 10 IU/mg is administered in combination with an uterotonic agent capable of promoting myometrial contractions of the uterus.

In one ~~aspect~~embodiment, there is provided a chemically modified heparin or heparan sulfate with an antifactor IIa activity of less than 10 IU/mg, an antifactor Xa activity of less than 10 IU/mg and an average molecular weight (Mw) from about 4.6 to about 6.9 kDa comprising:

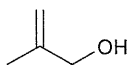
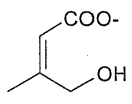
(i) polysaccharide chains essentially free of chemically intact saccharide sequences mediating the anticoagulant effect; and

(ii) polysaccharide chains corresponding to molecular weights between 1.2 and 12 kDa with a predominantly occurring disaccharide according to (Formula I),



(Formula I)

wherein,

R'=  or 

n is an integer from 2 to 20

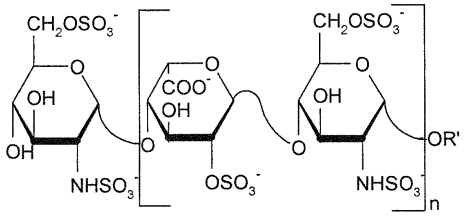
wherein the modified heparin or heparan sulfate comprises non-reducing end unsaturated glucosamines that are presented as signals in the interval of 5.0 to 6.5 ppm in a ^{1}H-NMR spectrum with an intensity (% ratio) of less than 4% in relation to the signal at 5.42 ppm from native heparin,

for use in combination with at least one uterotonic agent in the treatment of postpartum haemorrhage (PPH).

In another ~~aspect~~embodiment, there is provided a chemically modified heparin or heparan sulfate with an antifactor IIa activity of less than 10 IU/mg, an antifactor Xa activity of less than 10 IU/mg and an average molecular weight (Mw) from about 4.6 to about 6.9 kDa comprising:

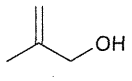
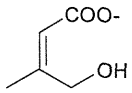
(i) polysaccharide chains essentially free of chemically intact saccharide sequences mediating the anticoagulant effect; and

(ii) polysaccharide chains corresponding to molecular weights between 1.2 and 12 kDa with a predominantly occurring disaccharide according to (Formula I),



(Formula I)

wherein,

R'=  or 

n is an integer from 2 to 20

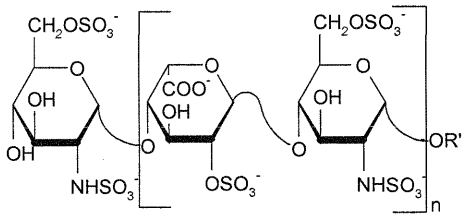
wherein the modified heparin or heparan sulfate comprises non-reducing end unsaturated glucosamines that are presented as signals in the interval of 5.0 to 6.5 ppm in a ^{1}H-NMR spectrum with an intensity (% ratio) of less than 4% in relation to the signal at 5.42 ppm from native heparin,

for use in combination with at least one uterotonic agent in the prevention of postpartum haemorrhage (PPH).

In another aspect, there is provided the use of a chemically modified heparin or heparan sulfate with an antifactor IIa activity of less than 10 IU/mg, an antifactor Xa activity of less than 10 IU/mg and an average molecular weight (Mw) from about 4.6 to about 6.9 kDa comprising:

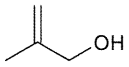
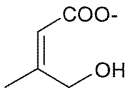
(i) polysaccharide chains essentially free of chemically intact saccharide sequences mediating the anticoagulant effect; and

(ii) polysaccharide chains corresponding to molecular weights between 1.2 and 12 kDa with a predominantly occurring disaccharide according to (Formula I),



(Formula I)

wherein,

R'=  or 

n is an integer from 2 to 20, and

(iii) having a distribution of polysaccharides and their corresponding molecular mass expressed as cumulative % of weight according to the table:

Molecular mass, kDa	Cumulative weight, %
>10	4-15
>8	10-25
>6	22-45
>3	>70

and at least one uterotonic agent selected from the group consisting of oxytocin or carbocetin, an ergot alkaloid or a prostaglandin

~~wherein the modified heparin or heparan sulfate comprises non-reducing end unsaturated glucosamines that are presented as signals in the interval of 5.0 to 6.5 ppm in a ^{1}H-NMR spectrum with an intensity (% ratio) of less than 4% in relation to the signal at 5.42 ppm from native heparin,~~

~~for use~~ in the manufacture of a medicament ~~for use in combination with at least one uterotonic agent in the treatment of~~ for treating postpartum haemorrhage (PPH), wherein the medicament is to be administered after delivery as an add-on therapy to a woman who has already been subjected to therapy with, said uterotonic agent.

Brief description of the figures

Figures 1A-1D show calcium ion influx in uterine muscle cells when treated with combinations of oxytocin and a chemically modified heparin (DF01) as defined according to the invention.

Description of the invention

It is to be understood that the terminology employed herein is used for the purpose of describing particular embodiments only and is not intended to be limiting the invention.

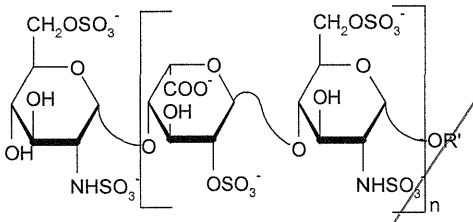
It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise.

Also, the term "about" is used to indicate a deviation of +/- 2 % of the given value, preferably +/- 5 %, and most preferably +/- 10 % of the numeric values, where applicable.

In one aspect of the present invention the term "postpartum haemorrhage (PPH)" is defined as a blood loss of about 500 ml or more after vaginal delivery and about 1000 ml or more after caesarian delivery. In yet an aspect of the present invention

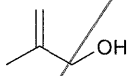
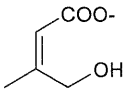
Claims

1. A chemically modified heparin or heparan sulfate with an antifactor IIa activity of less than 10 IU/mg, an antifactor Xa activity of less than 10 IU/mg and an average molecular weight (Mw) from about 4.6 to about 6.9 kDa comprising:
(i) polysaccharide chains essentially free of chemically intact saccharide sequences mediating the anticoagulant effect; and
(ii) polysaccharide chains corresponding to molecular weights between 1.2 and 12 kDa with a predominantly occurring disaccharide according to (Formula I),



(Formula I)

wherein,

R'=  or 

n is an integer from 2 to 20

wherein the modified heparin or heparan sulfate comprises non-reducing end unsaturated glucosamines that are presented as signals in the interval of 5.0 to 6.5 ppm in a ^{1}H-NMR spectrum with an intensity (% ratio) of less than 4% in relation to the signal at 5.42 ppm from native heparin,

for use in combination with at least one uterotonic agent in the treatment of postpartum haemorrhage (PPH).

2. The chemically modified heparin or heparan sulfate for use according to claim 1, wherein the PPH appears in a woman suffering from uterine atony.

3. The chemically modified heparin or heparan sulfate for use according to claim 1 or 2, wherein the PPH appears in a woman who has been induced into labor.

4. The chemically modified heparin or heparan sulfate for use according to claim 1 or 2, wherein the PPH appears in a woman who has experienced labor arrest.

5. The chemically modified heparin or heparan sulfate for use according to any one of claims 1-4, wherein the uterotonic agent is selected from the group consisting of oxytocin or an analogue of oxytocin, an ergot alkaloid, a prostaglandin or an analogue of prostaglandin.

6. The chemically modified heparin or heparan sulfate for use according to claim 5, wherein the uterotonic agent is oxytocin or an analogue of oxytocin.

7. The chemically modified heparin or heparan sulfate for use according to claim 6, wherein the uterotonic agent is oxytocin.

8. The chemically modified heparin or heparan sulfate for use according to claim 6, wherein the analogue of oxytocin is carbocetin.

9. The chemically modified heparin or heparan sulfate for use according to claim 5, wherein the uterotonic agent is a prostaglandin or an analogue of prostaglandin.

10. The chemically modified heparin or heparan sulfate for use according to claim 5, wherein the uterotonic agent is an ergot alkaloid.

11. The chemically modified heparin or heparan sulfate for use according any one of claims 1 to 10, wherein the predominantly occurring polysaccharide chains have between 6 and 12 disaccharide units with molecular weights from 3.6 to 7.2 kDa.

12. The chemically modified heparin or heparan sulfate for use according to any one of claims 1 to 11, wherein at least 70 % of the polysaccharide chains have a molecular weight above 3 kDa.

13. The chemically modified heparin or heparan sulfate for use according to any one of claims 1 to 12, having a distribution of polysaccharides and their corresponding molecular mass expressed as cumulative % of weight according to the table:

Molecular mass, kDa	Cumulative weight, %
>10	4-15
>8	10-25
>6	22-45
>3	>70

14. The chemically modified heparin or heparan sulfate for use according to any one of claims 1 to 13, wherein the modified glucosamine signals are presented at 5.95 ppm and 6.15 ppm in the ^{1}H-NMR spectrum.

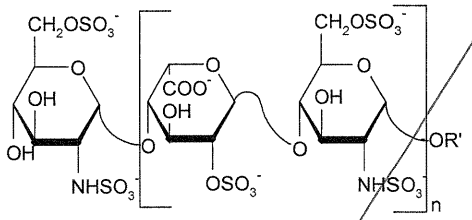
15. The chemically modified heparin or heparan sulfate for use according to claim 14, modified glucosamines comprise less than 1% of the total glucosamine content.

16. The chemically modified heparin or heparan sulfate for use according to any one of claims 1 to 15, wherein the chemically modified heparin or heparin sulfate is essentially free of intact non-sulfated iduronic and/or glucuronic acids.

17. The chemically modified heparin or heparan sulfate for use according to any one of claims 1-16, wherein the at least one chemically modified heparin or heparan sulfate is administered in a parenteral pharmaceutical preparation.

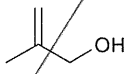
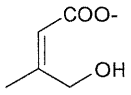
18. The chemically modified heparin or heparan sulfate for use according to any one of claims 1 to 17, wherein the chemically modified heparin or heparan sulfate is for use for as an add-on therapy to a woman who has already been subjected to therapy with an uterotonic agent.

19. A chemically modified heparin or heparan sulfate with an antifactor IIa activity of less than 10 IU/mg, an antifactor Xa activity of less than 10 IU/mg and an average molecular weight (Mw) from about 4.6 to about 6.9 kDa comprising:
(i) polysaccharide chains essentially free of chemically intact saccharide sequences mediating the anticoagulant effect; and
(ii) polysaccharide chains corresponding to molecular weights between 1.2 and 12 kDa with a predominantly occurring disaccharide according to (Formula I),



(Formula I)

wherein,

R'=  or 

n is an integer from 2 to 20

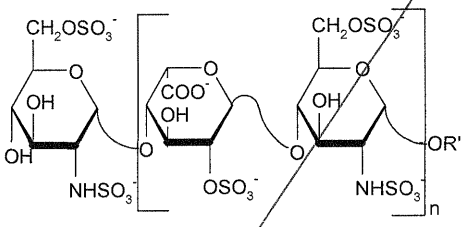
wherein the modified heparin or heparan sulfate comprises non-reducing end unsaturated glucosamines that are presented as signals in the interval of 5.0 to 6.5 ppm in a ^{1}H-NMR spectrum with an intensity (% ratio) of less than 4% in relation to the signal at 5.42 ppm from native heparin,

for use in combination with at least one uterotonic agent in the prevention of postpartum haemorrhage (PPH).

20. The chemically modified heparin or heparan sulfate for use according to claim 19, wherein the chemically modified heparin or heparan sulfate is for use for as an add-

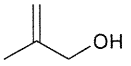
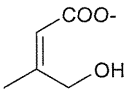
on therapy to a woman who has already been subjected to therapy with an uterotonic agent.

21. A chemically modified heparin or heparan sulfate with an antifactor IIa activity of less than 10 IU/mg, an antifactor Xa activity of less than 10 IU/mg and an average molecular weight (Mw) from about 4.6 to about 6.9 kDa comprising:
(i) polysaccharide chains essentially free of chemically intact saccharide sequences mediating the anticoagulant effect; and
(ii) polysaccharide chains corresponding to molecular weights between 1.2 and 12 kDa with a predominantly occurring disaccharide according to (Formula I),



(Formula I)

wherein,

R'=  or 

n is an integer from 2 to 20

wherein the modified heparin or heparan sulfate comprises non-reducing end unsaturated glucosamines that are presented as signals in the interval of 5.0 to 6.5 ppm in a ^{1}H-NMR spectrum with an intensity (% ratio) of less than 4% in relation to the signal at 5.42 ppm from native heparin,

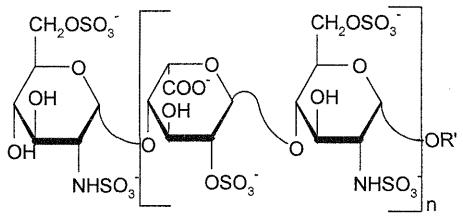
for use in the manufacture of a medicament for use in combination with at least one uterotonic agent in the treatment of postpartum haemorrhage.

22. The chemically modified heparin or heparan sulfate for use according to claim 23, wherein the chemically modified heparin or heparan sulfate is for use for as an add-on therapy to a woman who has already been subjected to therapy with an uterotonic agent.

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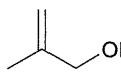
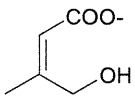
Claims

1. Use of a chemically modified heparin or heparan sulfate with an antifactor IIa activity of less than 10 IU/mg, an antifactor Xa activity of less than 10 IU/mg, and an average molecular weight (Mw) from about 4.6 and 6.9 kDa, comprising:
(i) polysaccharide chains essentially free of chemically intact saccharide sequences mediating the anticoagulant effect; and
(ii) polysaccharide chains corresponding to molecular weights between 1.2 and 12 kDa with a predominantly occurring disaccharide according to (Formula I),



(Formula I)

wherein,

R'=  or 

n is an integer from 2 to 20, and
(iii) having a distribution of polysaccharides and their corresponding molecular mass expressed as cumulative % of weight according to the table:

Molecular mass, kDa	Cumulative weight, %
>10	4-15
>8	10-25
>6	22-45
>3	>70

and at least one uterotonic agent selected from the group consisting of oxytocin or carbocetin, an ergot alkaloid or a prostaglandin

in the manufacture of a medicament for treating postpartum haemorrhage (PPH), wherein the medicament is to be administered after delivery as an add-on therapy to a woman who has already been subjected to therapy with, said uterotonic agent.

2. The use according to claim 1, wherein the PPH appears in a woman suffering from uterine atony.

3. The use according to claim 1 or 2, wherein the PPH appears in a woman who has been induced into labor.

4. The use according to claim 1 or 2, wherein the PPH appears in a woman who has experienced labor arrest.

5. The use according to claim 1, wherein the uterotonic agent is oxytocin or carbocetin.

6. The use according to claim 5, wherein the uterotonic agent is oxytocin.

7. The use according to claim 5, wherein the uterotonic agent is carbocetin.

8. The use according to claim 1, wherein the uterotonic agent is a prostaglandin.

9. The use according to claim 1, wherein the uterotonic agent is an ergot alkaloid.

10. The use according any one of claims 1 to 9, wherein the predominantly occurring polysaccharide chains have between 6 and 12 disaccharide units with molecular weights from 3.6 to 7.2 kDa.

11. The use according to any one of claims 1 to 10, comprising modified glucosamines present as signals in the interval of 5.0 to 6.5 ppm in a ^{1}H-NMR spectrum with an intensity (% ratio) of less than 4 % in relation to the signal at 5.42 ppm from native heparin.

12. The use according to claim 11, wherein the modified glucosamine signals are presented at 5.95 ppm and 6.15 ppm in the ^{1}H-NMR spectrum.

13. The use according to any one of claims 1 to 12, wherein the chemically modified heparin or heparin sulfate is essentially free of intact non-sulfated iduronic and/or glucuronic acids.

14. The use according to any one of claims 1-13, wherein the at least one chemically modified heparin or heparan sulfate is to be administered in a parenteral pharmaceutical preparation.