Haemostasis and Pregnancy

Reference ranges for pregnant women

What is known about this topic?

- **Pregnancy** is associated with **many haemostatic complications**.
- The impact of pregnancy on coagulation test results can impact accurate diagnosis and treatment; thereby limiting the value and use of established/normal coagulation reference ranges.
- Some previous studies on obstetric haemostatic reference intervals have reported conflicting results and most do not fulfil the International Federation of Clinical Chemistry (IFCC) recommendation for calculating reference values.

What does this study add?

- Gestational age-specific reference intervals for 20 haemostatic laboratory tests in 391 women during uncomplicated pregnancy, delivery, and postpartum according to IFCC guidelines.
- Coagulation factors II, V, X, XI, XII, PT, aPTT, antithrombin, and protein C are fairly stable during uncomplicated pregnancy, delivery, as well as during the postpartum period.
- D-dimer, fibrinogen and coagulation factors VII, VIII, and IX increase, and Protein S activity decreases to such an extent, even throughout an uncomplicated pregnancy, that gestational age-specific reference values are mandatory for correct evaluation. During pregnancy, Total Protein S, and Free protein S to a lesser extent, are the best test to unveil deficiency.
- The usefulness of measuring fibrinogen and D-dimer during pregnancy is doubtful.
- **In summary, gestational age-specific reference values are essential for the accurate interpretation of a subset of haemostatic tests during pregnancy, delivery, and postpartum.**

Gestational age-specific reference intervals (2.5th & 97.5th percentiles)

STAGO REAGENTS	Non pregnant expected values (Mean ±2SD)	13-20 WEEKS
PT (INR)		
STA®-SPA 50	0.9 - 1.2*	0.81 - 1.08
		n=120
STA®-Neoplastine® CI plus	0.9 - 1.2*	0.56 - 1.10
		n=121
APTT (sec)		
STA®-PTT Automate	28.9 - 38.1**	28 - 40
		n=536
STA®-C.K. Prest®	25.6 - 35.2**	28 - 36
		n=123
STA®-Cephascreen®	23.6 - 34.8**	26 - 34
		n=111
FIBRINOGEN (µM or g/l)		
STA®- Fibrinogen	5.8 - 11.8 µM**	8.5 - 15.6
	2 - 4 g/l**	2.9 - 5.3
		n=536
COAGULATION FACTORS (IU/ml)		
STA®- Deficient II	0.70 - 1.30**	0.80 - 1.18
		n=129
STA®- Deficient V	0.70 - 1.20**	0.57 - 1.22
		n=129
STA®- Deficient VII	0.55 - 1.70**	0.55 - 1.84
		n=128
STA®- Deficient VIII	0.60 - 1.50**	0.82 - 2.91
		n=129
STA®- Deficient IX	0.60 - 1.50**	0.84 - 1.69
		n=127
STA®- Deficient X	0.70 - 1.20**	0.75 - 1.25
		n=127
STA®- Deficient XI	0.60 - 1.50**	0.52 - 1.80
		n=128
STA®- Deficient XII	0.60 - 1.50**	0.81 - 1.87
		n=127
COAGULATION INHIBITORS (IU/ml)		
STA®-Stachrom® AT III	0.80 - 1.20**	0.74 - 1.15
		n=536
STA®-Stachrom® Protein C	0.70 - 1.30**	0.80 - 1.45
		n=537
STA®-Staclot® Protein S	0.57 - 1.21**	0.34 - 0.93
		n=122
STA®-Liatest® free Protein S	0.50 - 1.34**	0.37 - 0.79
		n=535
Asserachrom® Total Protein S	0.60 - 1.40**	0.55 - 1.00
		n=122
D-DIMERS (µg/ml)		
STA®- Liatest® D-Di	<0.5**	0.2 - 1.4
		n=537

* Expected value according to author recommendation - ** Expected value according to reagent package insert - *** Values different to the weeks 13-20 period (p<0.05)

STAGO REAGENTS	21-28 WEEKS	29-34 WEEKS
PT (INR)		
STA®-SPA 50	**0.60 - 1.02*** **	**0.79 - 1.03*** **
	n=63	n=41
STA®-Neoplastine® CI plus	**0.50 - 1.13**	**0.58 - 1.17**
	n=58	n=30
APTT (sec)		
STA®-PTT Automate	**28 - 39**	**27 - 38*** **
	n=365	n=175
STA®-C.K. Prest®	**28 - 38**	**28 - 37**
	n=51	n=28
STA®-Cephascreen®	**25 - 35**	**26 - 36**
	n=53	n=28
FIBRINOGEN (µM or g/l)		
STA®- Fibrinogen	**8.8 - 16.8*** **	**9.5 - 16.7*** **
	3.0 - 5.7* **	**3.2 - 5.7*** **
	n=365	n=175
COAGULATION FACTORS (IU/ml)		
STA®- Deficient II	**0.82 - 1.28**	**0.88 - 1.21**
	n=56	n=30
STA®- Deficient V	**0.57 - 1.28**	**0.48 - 1.29**
	n=56	n=30
STA®- Deficient VII	**0.43 - 2.24*** **	**0.99 - 2.11*** **
	n=58	n=31
STA®- Deficient VIII	**0.96 - 3.72*** **	**0.89 - 3.49*** **
	n=56	n=30
STA®- Deficient IX	**0.81 - 1.87*** **	**0.88 - 1.80*** **
	n=55	n=28
STA®- Deficient X	**0.82 - 1.35**	**0.82 - 1.43**
	n=58	n=31
STA®- Deficient XI	**0.58 - 1.66**	**0.50 - 1.73**
	n=58	n =31
STA®- Deficient XII	**0.66 - 2.22**	**0.92 - 2.18**
	n=55	n=28
COAGULATION INHIBITORS (IU/ml)		
STA®-Stachrom® AT III	**0.73 - 1.14**	**0.76 - 1.12**
	n=365	n=175
STA®-Stachrom® Protein C	**0.84 - 1.58**	**0.79 - 1.53**
	n =369	n =177
STA®-Staclot® Protein S	**0.35 - 0.81**	**0.25 - 0.85*** **
	n=58	n=31
STA®-Liatest® free Protein S	**0.37 - 0.71*** **	**0.31 - 0.64*** **
	n =368	n=177
Asserachrom® Total Protein S	**0.47 - 1.02**	**0.33 - 0.98**
	n=58	n=32
D-DIMERS (µg/ml)		
STA®- Liatest® D-Di	**0.3 - 1.7*** **	**0.3 - 3.0*** **
	n=369	n=178

* Expected value according to author recommendation - ** Expected value according to reagent package insert - *** Values different to the weeks 13-20 period (p<0.05)

STAGO REAGENTS	35-42 WEEKS	PARTUS
PT (INR)		
STA®-SPA 50	**0.78 - 0.99*** **	**0.55 - 0.99*** **
	n=142	n=139
STA®-Neoplastine® CI plus	**0.15 - 1.14**	**0.62 - 1.70*** **
	n=68	n=58
APTT (sec)		
STA®-PTT Automate	**27 - 37*** **	**26 - 38*** **
	n=358	n=192
STA®-C.K. Prest®	**28 - 37**	**26 - 40**
	n=72	n=41
STA®-Cephascreen®	**26 - 36**	**24 - 36**
	n=71	n=41
FIBRINOGEN (µM or g/l)		
STA®- Fibrinogen	**10.3 - 19.1*** **	**10.3 - 19.0*** **
	3.5 - 6.5* **	**3.5 - 6.5*** **
	n=358	n=143
COAGULATION FACTORS (IU/ml)		
STA®- Deficient II	**0.79 - 1.29**	**0.70 - 1.15**
	n=73	n=55
STA®- Deficient V	**0.53 - 1.27**	**0.09 - 1.35**
	n=73	n=55
STA®- Deficient VII	**0.87 - 2.51*** **	**0.96 - 3.30*** **
	n=71	n=31
STA®- Deficient VIII	**1.30 - 4.30*** **	**1.31 - 4.67*** **
	n=73	n=25
STA®- Deficient IX	**0.92 - 2.15*** **	**1.02 - 2.06*** **
	n=72	n=55
STA®- Deficient X	**0.76 - 1.41*** **	**0.74 - 2.02*** **
	n=71	n=54
STA®- Deficient XI	**0.60 - 1.40**	**0.54 - 1.97**
	n=71	n=54
STA®- Deficient XII	**0.88 - 1.97**	**0.86 - 2.10**
	n=72	n=54
COAGULATION INHIBITORS (IU/ml)		
STA®-Stachrom® AT III	**0.70 - 1.16**	**0.70 - 1.08*** **
	n=358	n=160
STA®-Stachrom® Protein C	**0.71 - 1.50*** **	**0.73 - 1.91*** **
	n=362	n=241
STA®-Staclot® Protein S	**0.25 - 0.86*** **	**0.14 - 0.59*** **
	n=72	n=54
STA®-Liatest® free Protein S	**0.31 - 0.67*** **	**0.32 - 0.72*** **
	n=361	n=241
Asserachrom® Total Protein S	**0.43 - 1.06**	**0.44 - 1.04**
	n=71	n=55
D-DIMERS (µg/ml)		
STA®- Liatest® D-Di	**0.4 - 3.1*** **	**0.7 - 7.6*** **
	n=362	n=242

* Expected value according to author recommendation - ** Expected value according to reagent package insert - *** Values different to the weeks 13-20 period (p<0.05)

STAGO REAGENTS	PARTUS +1 day	PARTUS +2 days
PT (INR)		
STA®-SPA 50	**0.58 - 0.99*** **	**0.57 - 1.03*** **
	n=135	n=85
STA®-Neoplastine® CI plus	**0.47 - 1.53**	**0.65 - 1.70*** **
	n=70	n=44
APTT (sec)		
STA®-PTT Automate	**28 - 38**	**28 - 39**
	n=222	n=139
STA®-C.K. Prest®	**27 - 41**	**27 - 37**
	n=59	n=35
STA®-Cephascreen®	**26 - 40*** **	**26 - 37**
	n=55	n=32
FIBRINOGEN (µM or g/l)		
STA®- Fibrinogen	**10.1 - 19.4*** **	**11.5 - 19.7*** **
	3.4 - 6.6* **	**3.9 - 6.7*** **
	n=218	n=139
COAGULATION FACTORS (IU/ml)		
STA®- Deficient II	**0.65 - 1.25*** **	**0.70 - 1.24**
	n=65	n=37
STA®- Deficient V	**0.53 - 1.35**	**0.57 - 1.58*** **
	n=65	n=33
STA®- Deficient VII	**0.92 - 2.46*** **	**0.91 - 2.29*** **
	n=59	n=36
STA®- Deficient VIII	**1.25 - 5.21*** **	**1.15 - 6.00*** **
	n=56	n=33
STA®- Deficient IX	**0.98 - 2.14*** **	**1.06 - 2.14*** **
	n=64	n=39
STA®- Deficient X	**0.72 - 1.48**	**0.82 - 1.41*** **
	n=66	n=39
STA®- Deficient XI	**0.43 - 1.76**	**0.62 - 1.71**
	n=66	n=39
STA®- Deficient XII	**0.77 - 2.17**	**0.97 - 2.20**
	n=63	n=39
COAGULATION INHIBITORS (IU/ml)		
STA®-Stachrom® AT III	**0.64 - 1.09*** **	**0.66 - 1.19**
	n=220	n=139
STA®-Stachrom® Protein C	**0.82 - 1.72*** **	**0.88 - 1.69*** **
	n=255	n=157
STA®-Staclot® Protein S	**0.22 - 0.54*** **	**0.30 - 0.81*** **
	n=67	n=38
STA®-Liatest® free Protein S	**0.31 - 0.73*** **	**0.37 - 0.86**
	n=255	n=157
Asserachrom® Total Protein S	**0.43 -1.00*** **	**0.55 - 0.98**
	n=67	n=37
D-DIMERS (µg/ml)		
STA®- Liatest® D-Di	**0.8 - 12.8*** **	**0.5 - 10.9*** **
	n=255	n=157

* Expected value according to author recommendation - ** Expected value according to reagent package insert - *** Values different to the weeks 13–20 period (p<0.05)

Results of coagulation assays are system and reagent dependent. Gestational age-specific reference ranges must therefore be developed for each combination to facilitate accurate diagnosis of samples taken from pregnant women. In addition, published data confirm that reference ranges generated using a specific reagent/ coagulometer combination cannot be applied to other any reagent/ coagulometer systems.

The results were generated at Gentofte Hospital, Copenhagen, Denmark (Prof. Steen Stender) from **391 pregnant women without any complications** during pregnancy, vaginal delivery, or postpartum period. Plasma samples were obtained at gestational weeks 13–20, 21–28, 29–34, 35–42, at active labor, and on postpartum days 1 and 2.

Reference intervals for each gestational period were calculated for **20 coagulation parameters** on STA-R Evolution® analyser and automated reagents (except total Protein S measured by ELISA).

For each test/reagent, the first row shows the 2.5% and 97.5% percentiles of the population. The second row shows the number of individual samples.

Data adapted from P B. Szecsi et al - Thromb Haemost 2010; 103: 718–727

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