

## Policy

# Clinical Guideline

## Management of Women with a Low PAPP-A and Normal Chromosomes

**Policy developed by:** SA Maternal & Neonatal Community of Practice  
**Approved SA Health Safety & Quality Strategic Governance Committee on:**  
19 April 2016  
**Next review due:** 19 April 2019

**Summary** Guideline for the management of women with a low PAPP-A and normal chromosomes

**Keywords** Clinical guideline, management of women with a low PAPP-A and normal chromosomes, papp-a, first trimester screening, pregnancy associated plasma protein a, nuchal translucency, fetal biometry, chromosomes, normal chromosomes, uterine artery doppler, first trimester combined screening, mom, fb-hcg, samsas, faster study, human chorionic gonadotrophin

**Policy history** Is this a new policy? **Y**  
Does this policy amend or update an existing policy? **Y v1.0**  
Does this policy replace an existing policy? **N**  
If so, which policies?

**Applies to** All SA Health Portfolio

**Staff impact** All Clinical, Medical, Nursing, Allied Health, Emergency, Dental, Mental Health, Pathology

**PDS reference** CG152

### Version control and change history

Version	Date from	Date to	Amendment
1.0	11 July 14	19 April 2016	Original version
2.0	19 April 2016	current	

## Note

This guideline provides advice of a general nature. This statewide guideline has been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. The guideline is based on a review of published evidence and expert opinion.

Information in this statewide guideline is current at the time of publication.

SA Health does not accept responsibility for the quality or accuracy of material on websites linked from this site and does not sponsor, approve or endorse materials on such links.

Health practitioners in the South Australian public health sector are expected to review specific details of each patient and professionally assess the applicability of the relevant guideline to that clinical situation.

If for good clinical reasons, a decision is made to depart from the guideline, the responsible clinician must document in the patient's medical record, the decision made, by whom, and detailed reasons for the departure from the guideline.

This statewide guideline does not address all the elements of clinical practice and assumes that the individual clinicians are responsible for discussing care with consumers in an environment that is culturally appropriate and which enables respectful confidential discussion. This includes:

- The use of interpreter services where necessary,
- Advising consumers of their choice and ensuring informed consent is obtained,
- Providing care within scope of practice, meeting all legislative requirements and maintaining standards of professional conduct, and
- Documenting all care in accordance with mandatory and local requirements

### *Explanation of the aboriginal artwork:*

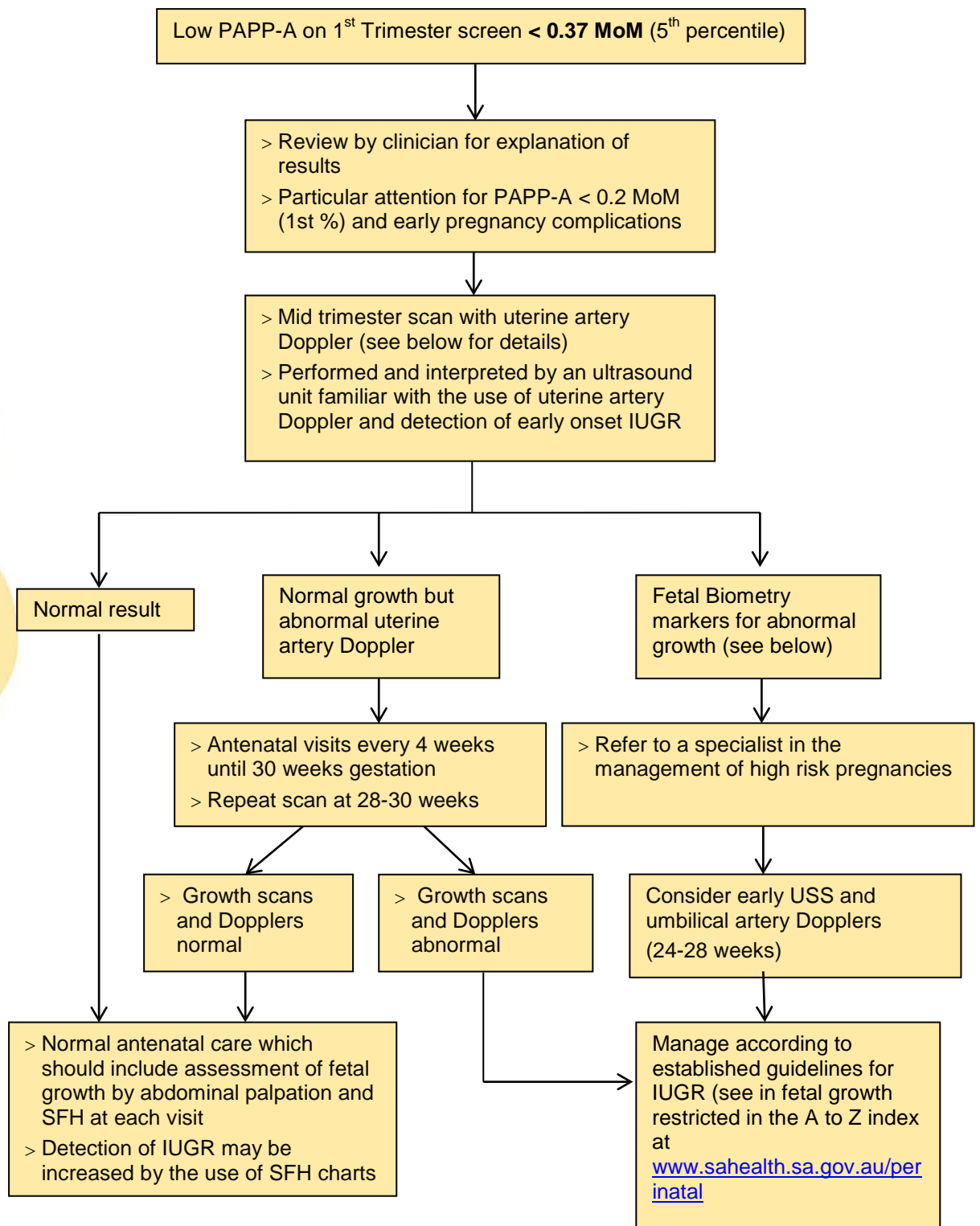
The aboriginal artwork used symbolises the connection to country and the circle shape shows the strong relationships amongst families and the aboriginal culture. The horse shoe shape design shown prior to the generic statement symbolises a woman and those enclosing a smaller horse shoe shape depicts a pregnant women. The smaller horse shoe shape in this instance represents the unborn child. The artwork shown before the specific statements within the document symbolises a footprint and demonstrates the need to move forward together in unison.



***Australian Aboriginal Culture is the oldest living culture in the world yet Aboriginal people continue to experience the poorest health outcomes when compared to non-Aboriginal Australians. In South Australia, Aboriginal women are 2-5 times more likely to die in childbirth and their babies are 2-3 times more likely to be of low birth weight. The accumulative effects of stress, low socio economic status, exposure to violence, historical trauma, culturally unsafe and discriminatory health services and health systems are all major contributors to the disparities in Aboriginal maternal and birthing outcomes. Despite these unacceptable statistics the birth of an Aboriginal baby is a celebration of life and an important cultural event bringing family together in celebration, obligation and responsibility. The diversity between Aboriginal cultures, language and practices differ greatly and so it is imperative that Perinatal services prepare to respectively manage Aboriginal protocol and provide a culturally positive health care experience for Aboriginal people to ensure the best maternal, neonatal and child health outcomes.***

# Management of women with a low PAPP-A and normal chromosomes

## Management of PAPP-A below the 5<sup>th</sup> percentile (< 0.37 MoM)



# Management of women with a low PAPP-A and normal chromosomes

## Introduction

- > All women should be offered the First Trimester Combined Screening between 9 and 14 weeks, with adequate pre-test counselling
  - > This combined screen measures maternal serum levels of free beta-human chorionic gonadotrophin (fb-HCG) and pregnancy-associated plasma protein-A (PAPP-A) at 9–13<sup>6</sup> weeks gestation along with nuchal translucency (NT) in mm by ultrasound at 11–13 weeks gestation. In combination with background risks such as maternal age, weight and gestational age, these measurements produce a risk estimate of the fetus having Down's syndrome or Trisomy 18<sup>1</sup>
  - > For pregnancies at increased risk, prenatal diagnostic testing via chorionic villus sampling or amniocentesis, can be offered

## PAPP-A

- > PAPP-A is a large glycoprotein produced by the placenta and decidua thought to have several functions including:
  - > Prevention of recognition of the fetus by the maternal immune system
  - > Matrix mineralisation
  - > Angiogenesis
- > A low PAPP-A is descriptive of poor early placentation and may result in adverse pregnancy outcomes such as<sup>2,3</sup>:
  - > Mid trimester miscarriage
  - > Fetal growth restriction
  - > Intrauterine fetal death
  - > Preterm birth
  - > Preeclampsia
- > Assisted reproductive technology (ART) pregnancies have reduced first trimester screening PAPP-A levels leading to an increased likelihood of receiving a false-positive result and having a chorionic villus sampling /amniocentesis. Lower PAPP-A may reflect impairment of early implantation with some forms of ART<sup>4</sup>
- > An abnormal PAPP-A is defined as a maternal serum PAPP-A concentration < 5<sup>th</sup> percentile, with increased frequency of adverse obstetrical outcomes noted below this level<sup>5</sup>
- > Although the risk of pregnancy complications is increased with PAPP-A < 5<sup>th</sup> percentile, a PAPP-A less than the 1<sup>st</sup> percentile offers a particular significant risk to the pregnancy<sup>6</sup>
- > **NB:** Accurate maternal weight should be confirmed upon return of the first trimester screen result as this has significant effect of PAPP-A concentrations

## FASTER study<sup>5</sup>

- > First and Second Trimester Evaluation of Risk trial (FASTER)
- > Prospective multi-centre study by the American National Institute of Child Health and Human Development (34,411 unselected population enrolled for this study)
- > Low PAPP-A the most common marker to be associated with adverse pregnancy outcome
  - > Low PAPP-A in the FASTER Study was defined as < 5<sup>th</sup> percentile. In the FASTER study this was 0.4 MoM. However the 5<sup>th</sup> percentile in the SAMSAS data is 0.37 MoM and this is the cut off that is relevant for South Australia
  - > For more information on the FASTER study, see Appendix 1 below

ISBN number:  
Endorsed by:  
Last Revised:

978-1-74243-084-3  
South Australian Maternal & Neonatal Community of Practice  
19/4/16

# Management of women with a low PAPP-A and normal chromosomes

## SAMSAS 2012 data of % of low PAPP-A

> It is recommended, where possible, to use local data when compiling percentiles

MoM	% SA Confinements Tested 2012
$\leq 0.4$ MoM	8%
<b><math>\leq 0.37</math> MoM</b>	<b>5%</b>
$\leq 0.3$ MoM	3%
<b><math>\leq 0.2</math> MoM</b>	<b>1%</b>

Data obtained from personal communication, SAMSAS December 2013

## Timing of investigations

- > The second trimester ultrasound offers an opportunity for further screening for IUGR and thus adjusting care pathways
- > When deciding on antenatal obstetric management, the obstetric team needs to know at what time during the pregnancy abnormal growth patterns occur with early screening tests outside the normal range
- > Several studies in women with low first trimester serum PAPP-A have demonstrated abnormal growth patterns beginning in the second trimester

## Fetal biometry

- > Fetal biometry at the morphology ultrasound may demonstrate markers for fetal growth restriction<sup>8</sup>. A combination of low PAPP-A and early fetal growth restriction increases the risk of adverse pregnancy outcomes by almost six-fold<sup>9</sup>
- > The following second trimester fetal biometry markers for abnormal growth should be used in conjunction with PAPP-A  $< 5^{\text{th}}$  percentile to define this high risk population
  - > EFW  $< 2.5$  percentile for gestation<sup>8</sup>
  - > average fetal biometry on ultrasound age more than 7 days smaller than well-established dates (LMP and 12 week scan)
  - > HC:AC ratio  $> 90^{\text{th}}$  percentile for gestational age

## Uterine artery Dopplers

- > Uterine Artery Dopplers at the morphology allow further stratification of risk of IUGR in women with a low PAPP-A<sup>10</sup>

### < 1st percentile of MOM $\leq 0.2$ MoM

- > Using extreme levels of fetoplacental proteins ( $< 1^{\text{st}}$  percentile)
  - > 20% of women had abnormal uterine Doppler (as compared to 5% in general population) at 22-24 weeks of gestation.
  - > 65% of women with extremes of fetoplacental proteins and abnormal uterine Doppler had adverse pregnancy outcome (Low birth weight, hypertension, preterm birth or fetal loss) as compared to 34% with normal uterine artery Doppler

## Management

- > The cut off for increased risk should be set at the  $5^{\text{th}}$  percentile (0.37 MoM) accordi

ISBN number: 978-1-74243-084-3  
 Endorsed by: South Australian Maternal & Neonatal Community of Practice  
 Last Revised: 19/4/16



# Management of women with a low PAPP-A and normal chromosomes

latest data from SAMSAS

- > Confirmation of accurate maternal weight on the SAMSAS report. (high BMI will artificially lower the PAPP-A MoM). If the report does not have appropriate maternal weight, contact SAMSAS with the correct weight and the result will be readjusted
- > Women who have a low PAPP A on 1<sup>st</sup> trimester screening should be counselled by the medical practitioner ordering the test about the risk of complications of pregnancy associated with low PAPP-A
- > Women with a PAPP-A < 1<sup>st</sup> percentile require particular attention because of the risk of mid trimester miscarriage. It is suggested that they are followed up by their medical practitioner at 16-17 weeks with fetal heart auscultation
- > **Aboriginal Women should be referred to an Aboriginal Health Professional to support their care.**



## Mid trimester ultrasound

- > Book routine morphology ultrasound (usually at 19 weeks gestation)
- > Written referral to the imaging unit should include information on any first trimester screen result with mention of PAPP-A < 5<sup>th</sup> percentile (0.37 MoM)
- > Imaging unit should have experience in performing and interpreting uterine artery Doppler and subtle fetal biometry abnormalities as described above
  - > For those pregnancies with PAPP-A < 5<sup>th</sup> percentile (0.37 MoM) morphology ultrasound should include an assessment of uterine artery Doppler

### Ultrasound assessment of uterine artery Doppler<sup>11</sup>

- > Abnormal uterine Doppler:
  - > Average RI (Left and Right) > 0.70
  - > Average RI (Left and Right) > 0.65 with unilateral diastolic notch
  - > Bilateral notches
- > Ultrasound report should document location of placenta
  - > Central, anterior or posterior
  - > Right lateral
  - > Left lateral

- > Any early growth abnormalities
  - > AC < 10<sup>th</sup> percentile
  - > Average ultrasound age > 7 days different from established dates

## Normal mid trimester scan

- > If the mid trimester scan is normal, reassure the woman that the likelihood of adverse outcomes approximates the normal population. The woman requires normal surveillance for fetal growth:
  - > At each antenatal visit, measure the symphysis fundal height (SFH) and chart on the SFH graph
  - > SFH measurement must be taken from the top of the fundus to the fixed point at the superior edge of the pubic symphysis. Measure along the fetal axis using a non-elastic tape measure<sup>5</sup>

ISBN number:  
Endorsed by:  
Last Revised:

978-1-74243-084-3  
South Australian Maternal & Neonatal Community of Practice  
19/4/16

# Management of women with a low PAPP-A and normal chromosomes

- > IUGR is suggested by measurements under the 10<sup>th</sup> percentile for gestation or when the SFH measurements are crossing percentile lines in a negative direction
- > Diagnostic accuracy may be improved by the use of customised growth charts<sup>12,13</sup>
- > If unable to accurately measure SFH (e.g. Women who have a high BMI), an ultrasound may be useful to calibrate SFH at around 28-30 weeks gestation
- > For further information, see fetal growth restricted guideline in the A to Z index at [www.sahealth.sa.gov.au/perinatal](http://www.sahealth.sa.gov.au/perinatal)
- > If clinical growth is normal at term, there is no indication for early induction and timing of delivery is dictated by normal obstetric indications
- > Continuous fetal heart rate monitoring once in established labour

## Normal growth and abnormal uterine Dopplers on mid trimester scan

- > Consider an ultrasound at 28 - 30 weeks of gestation to assess fetal growth, umbilical artery Dopplers and AFI
- > If IUGR is suggested by this ultrasound refer to the fetal growth restricted guideline in the A to Z index at [www.sahealth.sa.gov.au/perinatal](http://www.sahealth.sa.gov.au/perinatal) for further management
- > If growth is symmetrical and tracking parallel to the percentile lines then the risk of IUGR returns to the background risk, and therefore the woman may have routine antenatal care as described above

## Abnormal growth and normal Dopplers on mid trimester scan

- > These women are at increased risk of early onset IUGR and fetal demise
- > Consider an ultrasound at 24 - 28 weeks of gestation to assess fetal growth, umbilical artery Dopplers and AFI
- > If there is persistent evidence of early onset IUGR, further management is suggested in the fetal growth restricted guideline in the A to Z index at [www.sahealth.sa.gov.au/perinatal](http://www.sahealth.sa.gov.au/perinatal)
- > If the growth trajectory returns to normal the frequency of scans may be decreased or even stopped

## Abnormal growth and Dopplers on mid trimester scan

- > These women are at increased risk of early onset IUGR and fetal demise. They should be managed in conjunction with a specialist obstetrician familiar with the management of high risk pregnancies
- > Consider an ultrasound for growth Dopplers and AFI at 24-26 weeks
- > If there is persistent evidence of early onset IUGR, further management is suggested in the fetal growth restricted guideline in the A to Z index at [www.sahealth.sa.gov.au/perinatal](http://www.sahealth.sa.gov.au/perinatal)
- > If the growth trajectory returns to normal the frequency of scans may be decreased or even stopped

## Hypertensive disorders

- > Women with a low PAPP-A with abnormal uterine artery Dopplers are at risk of early onset pre-eclampsia. These women, with no other risk factors, should be seen more frequently after 20 weeks gestation. They should be seen at least every 4 weeks until 30 weeks gestation and more frequently if there are signs of pre-eclampsia

## References

# Management of women with a low PAPP-A and normal chromosomes

1. Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L et al. First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS). *Health Technol Assess* 2003; 7:1–77.
2. Gagnon A, Wilson RD, Audibert F, Allen VM, Blight C, Brock JA, et al. Obstetrical complications associated with abnormal maternal serum markers analytes. *J Obstet Gynaecol Can.* 2008; 30:918–49.
3. Yaron Y, Heifetz S, Ochshom Y, Lehavi O, Orr-Urtreger A. Decreased first trimester PAPP-A is a predictor of adverse pregnancy outcome. *PrenatDiagn*2002; 22:778-82.
4. Amor DJ, Xu JX, Halliday JL, Francis I, Healy DL et al. Pregnancies conceived using assisted reproductive technologies (ART) have low levels of pregnancy-associated plasma protein-A (PAPP-A) leading to a high rate of false-positive results in first trimester screening for Down syndrome. *Hum Reprod* 2009; 24: 1330-1338.
5. Dugoff L., Hobbins JC, Malone FD et al. First Trimester maternal serum PAPP-A and free-beta subunit human chorionic gonadotropin concentrations and nuchal translucency are associated with obstetric complications: A population-based screening study (The FASTER Trial). *AJOG.* 2004; 191:1446-51.
6. Krantz D, Goetzl L, Simpson JL. Association of extreme first-trimester free human chorionic gonadotropin-beta, pregnancy-associated plasma protein A, and nuchal translucency with intrauterine growth restriction and other adverse pregnancy outcomes. *AJOG* 2004; 191:1452.
7. Scott F. et al. Pregnancy outcome in the setting of extremely low first trimester PAPP-A levels. *ANZJOG*2009; 49: 258–262.
8. Fox NS, Shalom D, Chasen ST. Second-trimester fetal growth as a predictor of poor obstetric and neonatal outcome in patients with low first-trimester serum pregnancy-associated plasma protein-A and a euploid fetus. *Ultrasound Obstet Gynecol* 2009; 33: 34–38.
9. Kirkegaard I, Henriksen B, Uldbjerg N. Early fetal growth, PAPP-A and free  $\beta$ -hCG in relation to risk of delivering a small-for-gestational age infant. *Ultrasound Obstet Gynecol* 2011; 37: 341–347.
10. Filippi E, Staughton J, Peregrine E, Jones P, Huttly W, Peebles DM et al. Uterine artery Doppler and adverse pregnancy outcome in women with extreme levels of fetoplacental proteins used for Down syndrome screening. *Ultrasound Obstet Gynecol* 2011; 37: 520–527.
11. Kurdi W, Campbell S, et al. The role of color Doppler imaging of the uterine arteries at 20 weeks gestation in stratifying antenatal care. *Ultrasound Obstet Gynecol* 1998;12:339-345.
12. Figueras F, Gardosi J. Intrauterine growth restriction: new concepts in antenatal surveillance, diagnosis and management. *AJOG* 2011; 204:288-300.
13. Roex A, Nikpoor P, Van Eerd E, Hodyl N, Dekker G. Serial plotting on customised fundal height charts results in doubling of the antenatal detection of small for gestational age fetuses in nulliparous women. *ANZJOG.* 2012; 52:78-82.

## Useful resources

Centre for Genetics education: Prenatal testing

**ISBN number:**

978-1-74243-084-3

**Endorsed by:**

South Australian Maternal & Neonatal Community of Practice

**Last Revised:**

19/4/16



# Management of women with a low PAPP-A and normal chromosomes

---

Fact sheet 17: Prenatal testing overview. Available from URL:  
<http://www.genetics.edu.au/Information/Genetics-Fact-Sheets/Prenatal-Testing-Overview-FS17>

Fact sheet 17b: First and second trimester screening. Available from URL:  
<http://www.genetics.edu.au/Information/Genetics-Fact-Sheets/FS17B.pdf>

National Health and Medical Research Council: Genetics in Family Medicine. Testing and pregnancy. Available from URL:  
[http://www.nhmrc.gov.au/files\\_nhmrc/file/your\\_health/egenetics/practioners/gems/sections/03\\_testing\\_and\\_pregnancy.pdf](http://www.nhmrc.gov.au/files_nhmrc/file/your_health/egenetics/practioners/gems/sections/03_testing_and_pregnancy.pdf)

South Australian Maternal Serum Antenatal Screening (SAMSAS). Available from URL:  
<http://www.wch.sa.gov.au/services/az/divisions/labs/geneticmed/samsas.html>

# Management of women with a low PAPP-A and normal chromosomes

## Appendix 1:

### FASTER Study<sup>5</sup>

- > Prospective multi-centre study by the American National Institute of Child Health and Human Development (34,411 unselected population enrolled for this study)
- > Low PAPP-A the most common marker to be associated with adverse pregnancy outcome
  - > Low PAPP-A in the FASTER Study was defined as < 5th percentile. In the FASTER study this was 0.4 MoM. However the 5th percentile in the SAMSAS data is 0.37 MoM and this is the cut off that is relevant (see above)
- > Dose level inverse relationship response

### PAPP A < 5th percentile

- > Increased risk of IUFD. This was predominately an early phenomenon
- > PPV for fetal loss < 24 week of 2.2
- > PPV for fetal loss > 24 weeks only 0.6
- > Increased risk of IUGR (BW < 10<sup>th</sup> percentile)
  - > PPV of almost 20%
- > False positive rate at around 5% for all adverse events reasonable with other first trimester screening tests

### PAPP-A < 1<sup>st</sup> percentile

- > PPV for fetal loss < 24 weeks of 4.5
- > PPV for fetal loss > 24 weeks only 0.8
- > LBW < 10<sup>th</sup> percentile - PPV of 26.3
- > LBW < 5<sup>th</sup> percentile - PPV of 15.8

### PAPP-A < 5<sup>th</sup> percentile

	OR	Sens	FP	PPV
<b>Loss &lt; 24 weeks</b>	<b>2.5</b>	<b>12.9</b>	<b>5.1</b>	<b>2.2</b>
PTB < 32 weeks	1.9	9.5	5.1	1.4
LBW < 10 <sup>th</sup> percentile	2.5	10.5	4.6	18.7
LBW < 5 <sup>th</sup> percentile	2.8	12.3	4.8	9.5
PE	1.5	7.9	5.2	3.5

### PAPP-A < 1<sup>st</sup> percentile

	OR	Sens	FP	PPV
<b>Loss &lt; 24 weeks</b>	<b>5.2</b>	<b>5.4</b>	<b>5.1</b>	<b>4.5</b>
PTB < 32 weeks	3.3	3.2	1.0	2.4
LBW < 10 <sup>th</sup> percentile	3.5	2.9	0.8	26.3
LBW < 5 <sup>th</sup> percentile	4.6	4.1	0.9	15.82
PE	NS	NS	1.1	4.2

- > When there was a normal second-trimester ultrasound examination in women with PAPP-A, only 4.8% were diagnosed with third trimester SGA (95% NPV)

ISBN number:

978-1-74243-084-3

Endorsed by:

South Australian Maternal & Neonatal Community of Practice

Last Revised:

19/4/16

# Management of women with a low PAPP-A and normal chromosomes

---

- > However, when the second-trimester ultrasound examination showed a marker for fetal growth restriction, these proportions were 38.9%

## Sensitivity and positive predictive value

- > A low PAPP-A level has low sensitivity for the prediction of adverse pregnancy outcome
- > However, these associations do exist at the lower end of the PAPP-A distribution
- > The majority of pregnant women with these adverse outcomes **do not have** a low PAPP-A
- > In addition, it has a low positive predictive value (PPV) as few patients with a low PAPP-A actually have an adverse outcome
  - > 89 % normal outcome with PAPP-A < 0.2 MoM<sup>7</sup>

# Management of women with a low PAPP-A and normal chromosomes

## Abbreviations

AFI	Amniotic fluid index
ART	Assisted reproductive technology
BMI	Body mass index
BW	Birth weight
CI	Confidence interval
FP	False positive
FASTER	First and Second Trimester Evaluation of Risk trial
fb-HCG	Free beta-human chorionic gonadotropin
IUGR	Intrauterine growth restriction
LBW	Low birth weight
MoM	Multiples of the median
NPV	Negative predictive value
NS	Not significant
NT	Nuchal translucency
OR	Odds ratio
PAPP-A	Pregnancy associated plasma protein A
PE	Pre-eclampsia
%	Percent(ile)
PPV	Positive predictive value
PTB	Preterm birth
SAMSAS	South Australian Maternal Serum Antenatal Screening
SA PPG	South Australian Perinatal Practice Guidelines
Sens	Sensitivity
SFH	Symphysio-fundal height

## Version control and change history

**PDS reference:** OCE use only

Version	Date from	Date to	Amendment
1.0	04 Feb 2014	19 April 2016	Original version
2.0	19 April 2016	Current	Reviewed

**ISBN number:**  
**Endorsed by:**  
**Last Revised:**

978-1-74243-084-3  
South Australian Maternal & Neonatal Community of Practice  
19/4/16