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PAPP-A Guideline

Introduction and Aim

Pregnancy associated plasma protein A (PAPP-A) is a placental glycoprotein produced by syncytial trophoblast of the placenta, which cleaves insulin-like growth factor binding protein 4 (IGFBP4) and is a positive regulator of insulin-like growth factors (IGFs)[1], potentially influencing fetal growth and wellbeing.

Studies have tested the hypothesis that low maternal serum levels of PAPP-A in the first trimester are prognostic factors for adverse pregnancy outcomes associated with poor placental function [2-6]. International Guidelines on "The Investigation and Management of the Small for Gestational Fetus" have recommended that pregnant women with a serum PAPP-A <0.4MoM (5th centile) in the first trimester receive increased ultrasound surveillance for fetal growth disorders[7].

Objectives

To reduce maternal and fetal mortality and morbidity by increased surveillance and intervention where appropriate

Scope

This policy applies to all healthcare professionals in all locations including those with honorary contracts

Equality Health Impact Assessment	*An Equality Health Impact Assessment (EHIA) has not been completed.*
Documents to read alongside this Procedure	*Antenatal Care* *GAP Guideline* *Small for Gestational Age Guideline*
Approved by	*Maternity Professional Forum and Obstetrics & Gynaecology Quality & Safety*

Accountable Executive or Clinical Board Director	*Ruth Walker, Executive Nurse Director*
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1.1.1.1.1.1 Disclaimer

If the review date of this document has passed please ensure that the version you are using is the most up to date either by contacting the document author or the Governance Directorate.

Summary of reviews/amendments

Version Number	Date of Review Approved	Date Published	Summary of Amendments
1	*07/06/2019*	*13/06/2019*	New Document
2	*11/06/2020*		Minor amendment prior to implementation on 22nd June 2020. Women will now be reviewed within all consultant clinics, rather than solely in a single consultant clinic.

1 Table of Contents

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2 Summary and purpose

- **A low level (< 5th centile) of the first trimester marker PAPP–A should be considered a major risk factor for delivery of a SGA neonate and a risk factor for other adverse pregnancy outcomes.**

- **To provide information on potential adverse outcome associated with a low PAPP-A for clinicians and parents.**

- **To provide a pathway for appropriate notification of results, referral for Consultant led care and a pathway for implementation of appropriate surveillance to prompt early identification and management of potential adverse outcomes.**

- **To reduce maternal and fetal mortality and morbidity by increased surveillance and intervention where appropriate.**

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3 Background

Pregnancy associated plasma protein A (PAPP-A) is a placental glycoprotein produced by syncytial trophoblast of the placenta, which cleaves insulin-like growth factor binding protein 4 (IGFBP4) and is a positive regulator of insulin-like growth factors (IGFs)[1], potentially influencing fetal growth and wellbeing.

Studies have tested the hypothesis that low maternal serum levels of PAPP-A in the first trimester are prognostic factors for adverse pregnancy outcomes associated with poor placental function [2-6]. International Guidelines on "The Investigation and Management of the Small for Gestational Fetus" have recommended that pregnant women with a serum PAPP-A <0.4MoM (5th centile) in the first trimester receive increased ultrasound surveillance for fetal growth disorders[7].

In a large series of 49 801 women at 11+0 to 13+6 weeks, low PAPP–A (but not beta HCG) was inversely associated with risk of being small for gestational age (SGA). Using a 5th centile (0.415 MoM) cut off, ORs for a SGA infant (birthweight < 10th centile) and severe SGA (birthweight < 3rd centile) were 2.7 and 3.66 respectively [1)].

In Birmingham Women's Hospital, a retrospective cohort study from 2011-2015 included over 12,000 women and found that there was a significant relationship between PAPP-A and adverse pregnancy outcome and after multivariable analysis (i.e. adjusting for other factors) there was a lower odds of SGA [adjusted odds ratio (OR) 0.87 (95% CI 0.85,0.90)], preterm birth <37 weeks (PTB) [OR 0.92 (95%CI 0.90,0.96)], pre-eclampsia (PE) [0.91 (95% CI 0.85,0.97)] and stillbirth [OR 0.72 (95% CI 0.53,0.99)] as PAPP-A increases [2].

This equated to the following rates of adverse outcome out of 1000 women:

	Background rates/1000 women	**Women with PAPP-A < 5th centile**	**Women with PAPP-A < 1st centile**
PET	29	39	17*
Miscarriage 12-24 weeks	57	14	34
Stillbirth	3	10	34
Perinatal death	7	15	34
Neonatal death	3	6	0*
Preterm delivery <37 weeks	74	17	339
SGA <10th customised centile	160	255	271

Table 1 Rates of Adverse Outcome per 1000 women

- the rates of PET and neonatal death are presumed to be lower in the PAPPA<1st centile group due to a significant number of pregnancies miscarrying or delivering preterm.

As a result of national recommendations for PAPP-A MoM to be included in the risk assessment for SGA in both the RCOG SGA guideline[3] and the Savings Babies' lives stillbirth care bundle[4], and analysis of pregnancies that have ended in stillbirth within the trust, Cardiff & Vale will offer all women with a PAPP-A <5th centile serial growth scans.

At present in UK practice, PAPP-A is only used as part of combined screening for fetal chromosome anomaly (trisomies 21,18 and 13) and not as a biomarker for adverse outcome. Before any test (either individual or as a model) is introduced in this capacity into practice there must be an assessment of the interventions that may be introduced e.g. increased surveillance or pharmacological, to ensure that screening in a population is justified and these interventions must be effective in the group identified as high risk via the test or

model. At present although Aspirin has been suggested as a possible intervention in certain groups (e.g. those at high risk of pre-eclampsia based on previous history) there is no evidence for the effectiveness in a group selected by either PAPP-A as a stand-alone test or a model including PAPP-A.

This SOP details the pathway for identifying low results and the process for ensuring all women receive appropriate antenatal care following a low PAPP-A level.

This pathway only applies to women with an isolated low PAPP-A i.e. whose combined test gives a low risk for trisomy 21, 18 and 13 and in whom the nuchal translucency was normal. If women are **high risk for chromosomal aberrations or had a NT > 3.5 mm** they should follow established pathways linking with fetal medicine. If further investigations / screening are normal with a low PAPP-A MoM they should have additional screening for SGA, this should be actioned at the mid trimester ANC appointment.

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4 Pathway (see flow charts Section 8.1 and 8.2):

The antenatal screening midwife will identify any women with a low PAPP-A Mom using a 0.415 MoM cut off as the 5th centile and 0.2 MoM the 1st centile.

1. The screening midwife will obtain the hospital clinic card and copy of the combined screening report pertaining to these results.

2. A PAPP-A MoM sticker will be placed on the alert sheet with the result documented and a written entry will be made into the hospital records and on E3.

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5 Implementation and Audit

This process will be implemented from 22nd June 2020.

A database will be kept by the screening midwife and an audit of the process will be conducted 6 months following the implementation of this pathway to assess compliance (see appendix 5).

Dr A Robb is the clinician responsible for this policy.

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6 References

1. Lawrence JB, Oxvig C, Overgaard MT, Sottrup-Jensen L, Gleich GJ, Hays LG, et al. The insulin-like growth factor (IGF)-dependent IGF binding protein-4 protease secreted by human fibroblasts is pregnancy-associated plasma protein-A. Proceedings of the National Academy of Sciences of the United States of America. 1999 Mar 16;96(6):3149-53.

2. Dugoff L, Hobbins JC, Malone FD, Porter TF, Luthy D, Comstock CH, 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). Am J Obstet Gynecol. 2004 Oct;191(4):1446-51.

3. Krantz D, Goetzl L, Simpson JL, Thom E, Zachary J, Hallahan TW, et al. 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. Am J Obstet Gynecol. 2004 Oct;191(4):1452-8.

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5. Barrett SL, Bower C, Hadlow NC. Use of the combined first-trimester screen result and low PAPP-A to predict risk of adverse fetal outcomes. Prenat Diagn. 2008 Jan;28(1):28-35.

6. Spencer CA, Allen VM, Flowerdew G, Dooley K, Dodds L. Low levels of maternal serum PAPP-A in early pregnancy and the risk of adverse outcomes. Prenat Diagn. 2008 Nov;28(11):1029-36.

7. Bilagi A, Burke DL, Riley RD, Mills I, Kilby MD, Morris RK. Association of maternal serum PAPP-A levels, nuchal translucency and crown rump length

in first trimester with adverse pregnancy outcomes: Retrospective cohort study. Submitted to BJOG August 2016.

8. RCOG. The Investigation and Management of the Small–for–Gestational–Age Fetus. Greentop Guideline NO 31: RCOG; 2014.

9. Saving Babies' Lives A Care Bundle for reducing stillbirth. NHS England Published 21/3/2016. https://www.england.nhs.uk/wp-content/uploads/2016/03/saving-babies-lives-car-bundl.pdf

7 Related guidance

- Saving Babies Lives Care bundle: Standard Operating Procedure
- IUGR Detection and Management of Small for Gestational Age Fetuses Guideline

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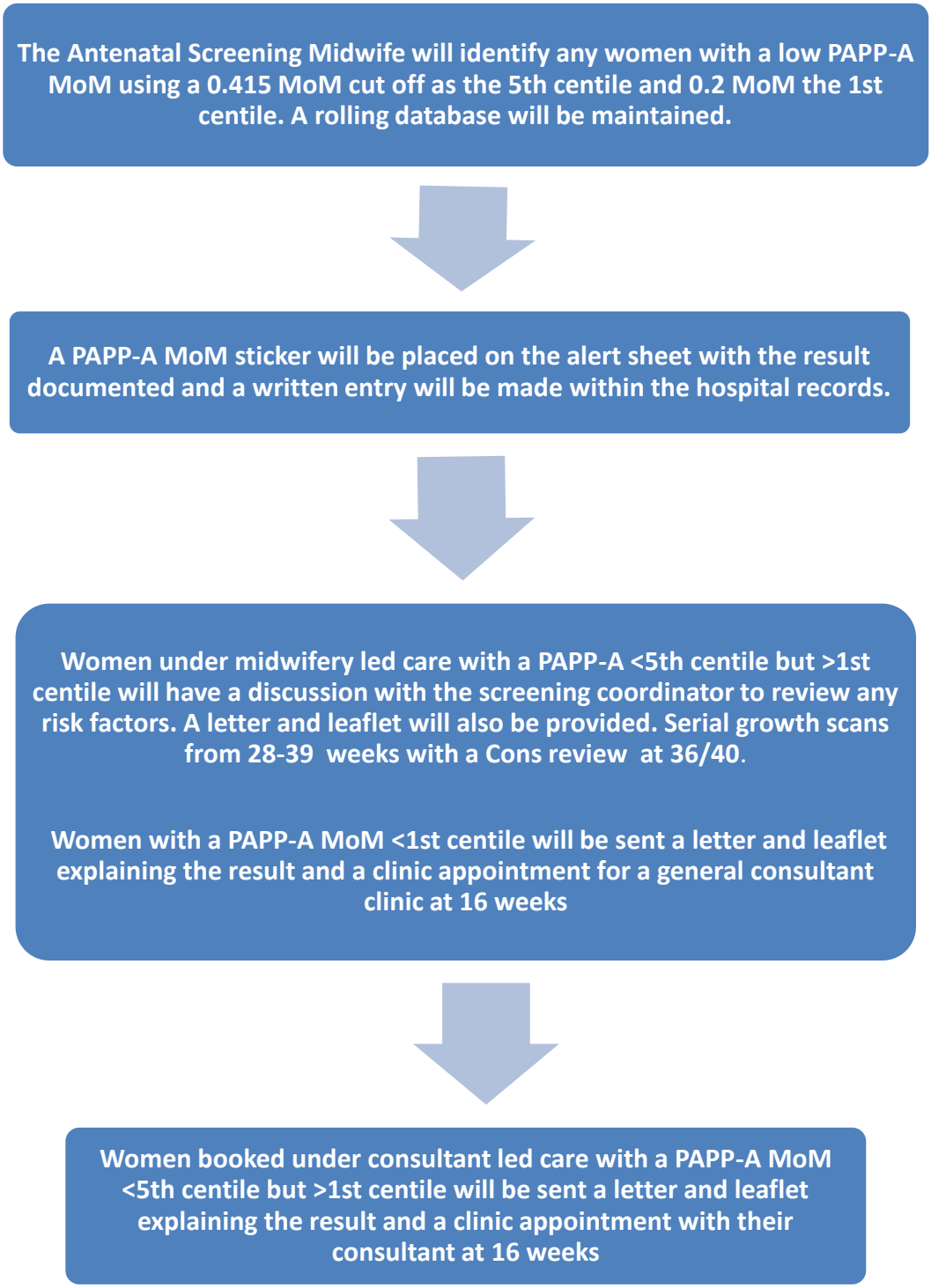
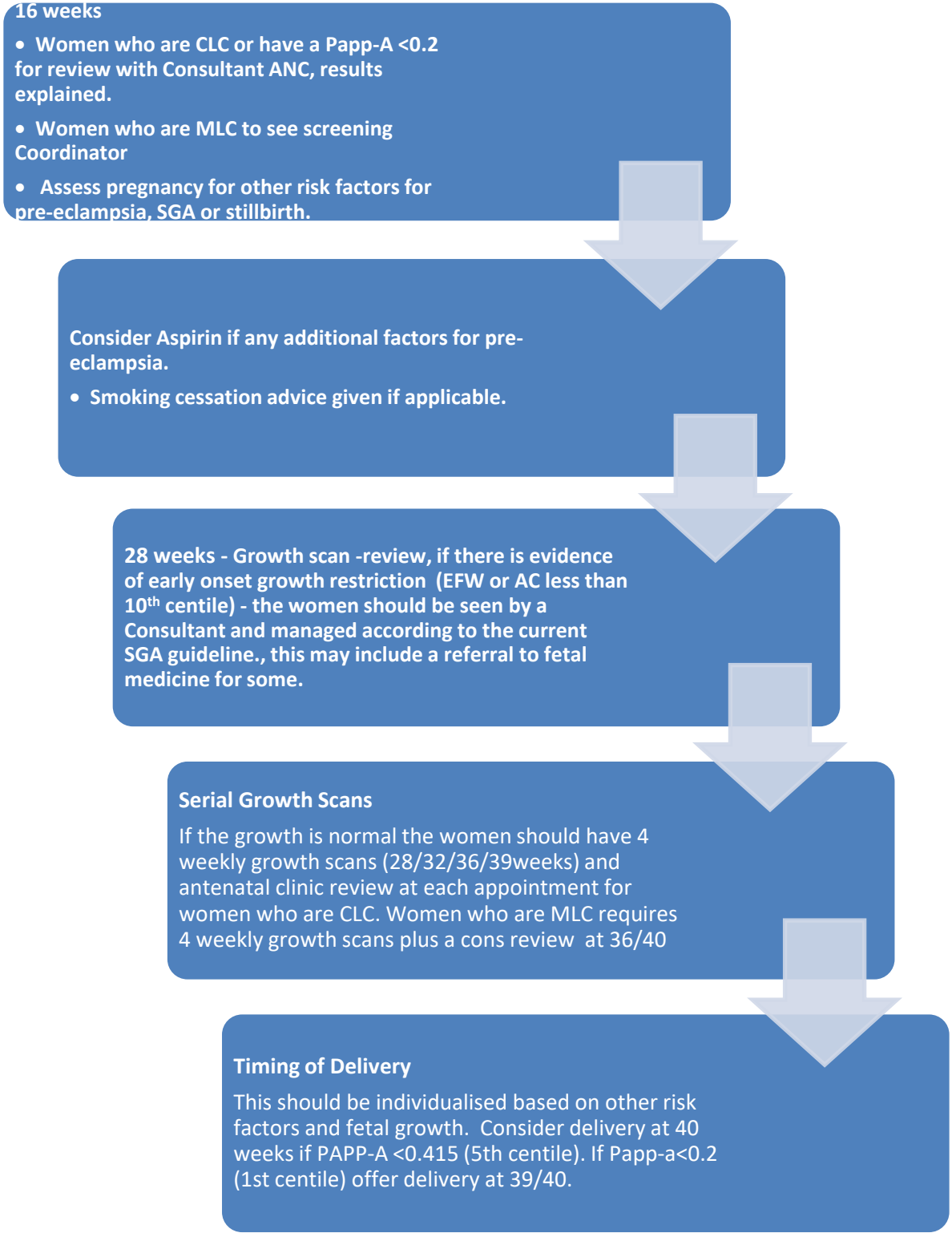
8 Appendices

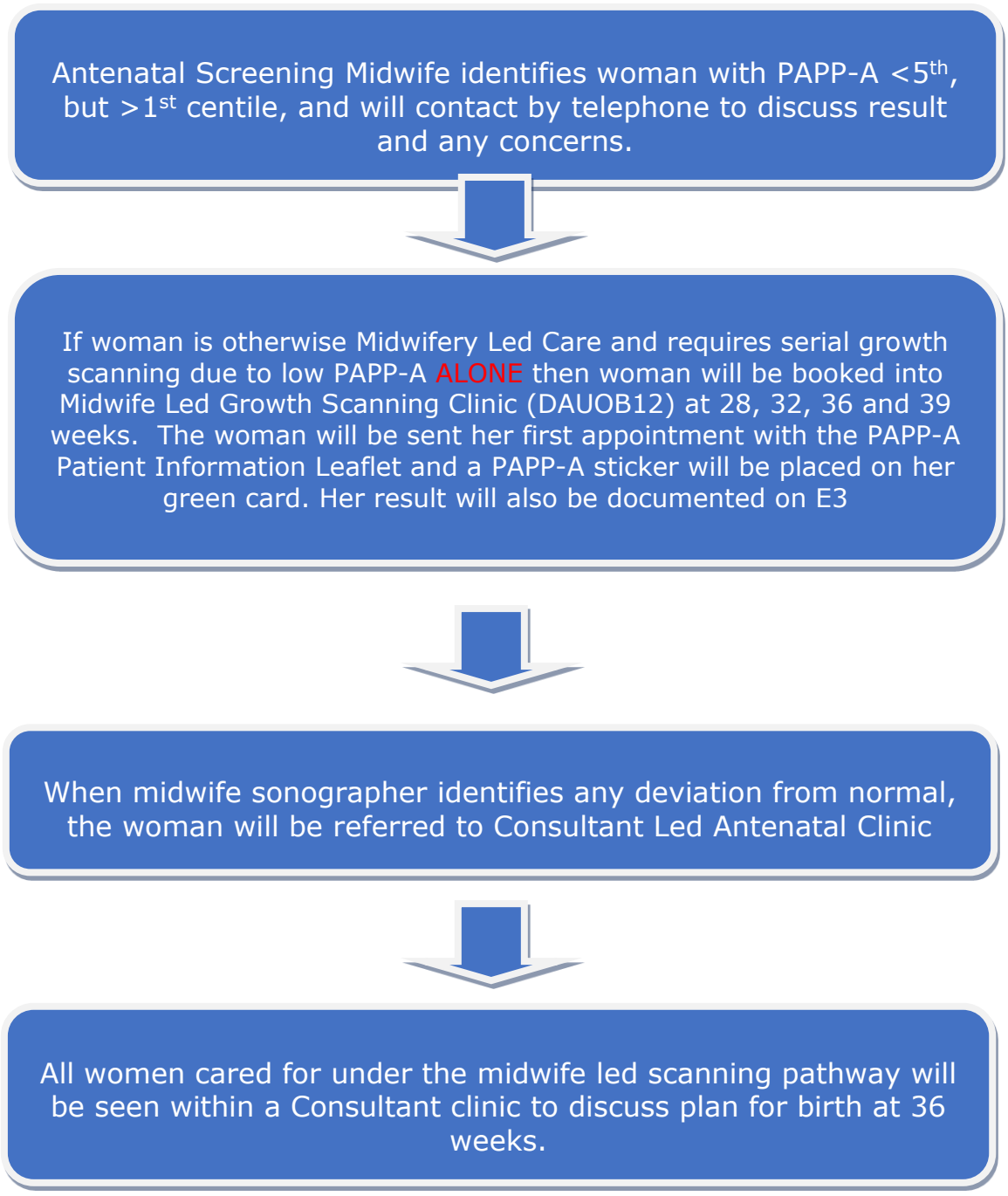
8.1 Appendix: Flowchart for the identification of women with low PAPP-A results



8.2 Appendix: Flowchart for Management of Women with low PAPP-A results



8.3 Appendix: Midwife Led Growth Scanning Pathway



8.4 Appendix:-Patient letter informing low PAPP-A result

Patient Details Date

Dear

Following your recent blood tests we have noted that one of your hormone levels is a little lower than we would expect and for that reason we would like to invite you to attend for a consultant appointment to discuss this further. A low level of hormone is sometimes associated with smaller babies, so we take the precaution of offering you extra scans during the pregnancy to monitor this; there is no cause for alarm.

Please do not hesitate to contact us if you would like further information on 02920 745265 (UHW) / 02920 716103 (UHL) between the hours of 9-5pm Monday to Friday.

Yours sincerely,

Natasha Thomas
Antenatal Screening Midwife

- This will be for all CLC women and women with a Papp-a <0.2
- All MLC women would have been phoned and information discussed
- Please always check E3

8.5 Appendix: Patient information leaflet for low PAPP-A results.

Information for Parents:

Low Pregnancy Associated Plasma Protein A (PAPP-A)

You have been given this leaflet as you have a low PAPP-A on the combined screening test.

What is PAPP-A?

Pregnancy associated plasma protein A (PAPP-A) is a hormone that is produced by the placenta in pregnancy. It is one of two hormones that are measured during the 12 week combined screening test.

Low levels of PAPP-A can be associated with Down's Syndrome (an extra chromosome 21), Edward's (extra chromosome 18) and Patau's syndrome (extra chromosome 13). If your baby has an increased risk for these chromosome differences, the antenatal screening midwife will have already contacted you before sending you this leaflet.

Studies have also shown that low PAPP-A may also be associated with small babies, early deliveries and pre-eclampsia (high blood pressure and protein in your urine). An unborn baby is small if, at that stage of pregnancy, his or her size or estimated weight on scan is in the lowest 10% of babies. This means the smallest ten out of every 100 babies. Because of this, national guidelines suggest that extra scans should be considered to check the growth of babies when a low PAPP-A level has been found.

What would being small mean for my baby?

If your baby is small but healthy, he or she is not at increased risk of complications. If your baby is growth restricted, there is an increased risk of stillbirth (the baby dying in the womb). The extra scans help us to identify those babies that are small and allow us to put in place extra monitoring as required and consider earlier delivery.

When will I have the extra scans?

We will then check your baby's growth, your baby's fluid levels and the blood flow in the placenta at 28 weeks and then at least every 4 weeks until delivery.

When we see you, will depend on your individual circumstances and be tailored to your specific needs. All women and their babies will have a personalised plan made with the doctors looking after them.

Sometimes you will be asked to attend our specialist growth clinic.

Is there anything I can do help my baby to grow well?

If you smoke, it is extremely important that you stop. Smoking can affect the placenta and the baby's growth. Your midwife can refer you for help to stop smoking.

Who can I speak to if I need further information?

You are welcome to phone one of the antenatal screening midwives if you have any queries or concerns. Receiving the news that you have low PAPP-A levels may cause anxiety but please be assured that the majority of babies will have normal growth and the pregnancy will progress normally.

Contact details

Antenatal Screening Midwife / Clinic Midwives 02920 745265 (UHW) / 02920 716103 (UHL)

Mon-Fri 9:00 – 17.00