Screening in Early Pregnancy for Adverse Perinatal Outcomes

Objectives: To provide advice on screening for adverse perinatal outcomes.

Outcomes: Improved detection and maternal and fetal outcomes from pre-eclampsia, fetal growth restriction (FGR)/small for gestational age (SGA), and pre-term birth.

Target audience: Health professionals responsible for providing maternity care, and patients.

Evidence: MEDLINE and the Cochrane Library were searched for randomised trials and cohort studies on prenatal screening for the adverse pregnancy outcomes pre-eclampsia, fetal growth restriction (FGR)/small for gestational age (SGA), pre-term birth and gestational diabetes (from July 2010 to March 2015).

Values: The evidence was reviewed by the writing group, and applied to local factors relating to Australia and New Zealand.

Background: This statement was first developed by RANZCOG’s Women’s Health Committee during 2014-15.

Funding: The development and review of this statement was funded by RANZCOG.

This statement has been developed and reviewed by the following writing group (brought together by Women’s Health Committee with the sole purpose of developing this statement):

- Professor Sue Walker (Mercy Hospital for Women)
- A/Prof Natasha Nassar (The University of Sydney)
- Dr Alison Fung (Mercy Hospital for Women)

This statement was reviewed by Women’s Health Committee and approved by the RANZCOG Board and Council.

A list of Women’s Health Committee Members can be found in Appendix A.

Disclosure statements have been received from all members of this committee.

The Committee acknowledges contributing authorship in Appendix B.

Disclaimer: This information is intended to provide general advice to practitioners. This information should not be relied on as a substitute for proper assessment with respect to the particular circumstances of each case and the needs of any patient. This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The document has been prepared having regard to general circumstances.

First endorsed by RANZCOG: July 2015
Current: July 2015
Review due: July 2018
Table of contents

1. Patient summary .......................................................................................................................... 3
2. Summary of recommendations ...................................................................................................... 3
3. Introduction ................................................................................................................................ 4
4. Discussion and recommendations ................................................................................................. 4

4.1 Pre-eclampsia ............................................................................................................................. 4
   4.1.1 The role of clinical assessment ....................................................................................... 5
   4.1.2 The role of ultrasound and biochemistry ......................................................................... 5
   4.1.3 How do these tests perform as screening tests for early onset pre-eclampsia? .......... 5
   4.1.4 What is the false positive rate?....................................................................................... 5
   4.1.5 Have the screening findings been validated in independent populations? .................. 6
   4.1.6 How do these tests perform as screening tests for early vs late onset pre-eclampsia? .... 6

4.2 Fetal Growth Restriction/Small for Gestational Age ................................................................. 7
   4.2.1 Definitions/diagnosis ...................................................................................................... 7
   4.2.2 Clinical significance ...................................................................................................... 7
   4.2.3 Clinical assessment in predicting FGR/SGA .................................................................... 7
   4.2.4 The role of biochemistry as clinical predictors of FGR/SGA .............................................. 8
   4.2.5 The role of uterine Doppler ultrasound as clinical predictors of FGR/SGA ......................... 9
   4.2.6 Conclusion and suggestions for management .................................................................... 9

4.3 Preterm birth ............................................................................................................................. 10
   4.3.1 The importance of preterm birth ................................................................................... 10
   4.3.2 Risk factors for Preterm Birth ........................................................................................ 10
   4.3.3 The Role of ultrasound Transvaginal Cervical Length as a Predictor of Spontaneous Preterm Birth .............................................................. 10
   4.3.4 The role of biochemical biomarkers as predictors of spontaneous preterm birth in asymptomatic women ......................................................... 10
   4.3.5 Conclusion and Recommendations .............................................................................. 11

5. Conclusion .................................................................................................................................. 11
6. References .................................................................................................................................. 12
7. Links to other College statements ............................................................................................... 13
8. Patient information ...................................................................................................................... 14

Appendices ....................................................................................................................................... 15

Appendix A Women’s Health Committee Membership .............................................................. 15
Appendix B Contributing Authors ................................................................................................. 15
Appendix C Overview of the Development and Review Process for this Statement ...................... 16
Appendix D Full Disclaimer ............................................................................................................ 17
1. Patient summary

Most pregnancies in Australia and New Zealand result in healthy outcomes. Structural or genetic abnormalities in the fetus are important adverse pregnancy outcomes, and are covered in the related documents *Prenatal screening and diagnosis of chromosomal and genetic abnormalities in the fetus in pregnancy (C-Obs 59)* and *Prenatal assessment of fetal structural abnormalities (C-Obs 60)*. Obstetric complications arising during pregnancy that are most likely to have an adverse impact on maternal and infant health are pre-eclampsia, impaired fetal growth (fetal growth restriction), and early (or preterm) birth. It would help if we could identify women at risk of pre-eclampsia, fetal growth restriction or preterm birth so that we could offer increased monitoring during pregnancy and, possibly, treatment. The greatest value would be if we could prevent these adverse outcomes from occurring. This statement summarises our current knowledge on screening tests that could be done in early pregnancy to identify women who might be at high risk of developing these disorders in later pregnancy.

2. Summary of recommendations

<table>
<thead>
<tr>
<th>Pre-eclampsia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation 1</strong></td>
</tr>
<tr>
<td>Routine screening of all pregnant women for pre-eclampsia risk factors is recommended to identify women at increased risk so that they can be offered aspirin, calcium (if diet deficient) and increased surveillance in pregnancy.</td>
</tr>
<tr>
<td><strong>Recommendation 2</strong></td>
</tr>
<tr>
<td>The place of combination ultrasound and serum markers as predictors of later pre-eclampsia awaits further clarification with some studies suggesting this test performs well as a predictor of severe early onset pre-eclampsia, which is rare. It does not perform well as a predictor of (the more common) late onset disease.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fetal growth restriction/small for gestational age</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation 3</strong></td>
</tr>
<tr>
<td>The predictive accuracy of biochemical biomarkers and ultrasound techniques in detecting fetuses at risk of growth restriction/small for gestational age has not provided auspicious results. The evaluation of a combination of certain biomarkers, Doppler ultrasound and maternal clinical risk factors in first trimester of pregnancy provides better results; further research will evaluate the predictive ability and cost effectiveness of these tests.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Preterm birth</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation 4</strong></td>
</tr>
<tr>
<td>All women should be assessed for risk factors for preterm birth. Women with a past history of spontaneous preterm birth should be offered progesterone to reduce their risk of recurrent preterm birth. For further guidance, please refer to College Statements <em>Progesterone Support of the Luteal Phase and Early Pregnancy (C-Obs 29a)</em> and <em>Progesterone: Use in the Second Trimester and</em></td>
</tr>
</tbody>
</table>
3. **Introduction**

Identifying women at high risk of adverse pregnancy outcomes such as pre-eclampsia, fetal growth restriction (FGR) and preterm birth would be valuable for a number of reasons. In some cases, there may be treatments available that could mitigate the risk of adverse outcomes; in others it may simply identify patients who warrant closer surveillance, or who may be candidates for research into these disorders. It is important that when new screening tests are introduced into practice that patients and clinicians are aware of the benefits and risks of screening, including the relevant false positive and false negative rates of screening.

4. **Discussion and recommendations**

4.1 **Pre-eclampsia**

Pre-eclampsia is a serious and important complication of pregnancy. Pre-eclampsia complicates 3-5% of pregnancies, and is estimated to be responsible for >50,000 maternal deaths and 500,000 infant deaths worldwide. Pre-eclampsia is responsible for 25% of fetal growth restriction, 33% of preterm births and 20% of NICU admissions.

Early pregnancy screening for pre-eclampsia is attractive because it is a disorder of high prevalence and disease burden, particularly in the developing world. Clinical screening of all pregnant women is recommended to identify women at increased risk of pre-eclampsia so that they can be offered aspirin, calcium (if diet deficient) and increased surveillance in pregnancy. The role of adding ultrasound and biochemistry to clinical risk factor scoring awaits clarification, given (i) the cost of screening, (ii) the challenges associated with widespread implementation, (iii) the modest detection rates on attempted validation in external populations and (iv) the relatively high false positive rate, which may heighten patient and clinician anxiety. Patients and clinicians electing to have first trimester ultrasound and biochemical
Prenatal Screening for Adverse Pregnancy Outcomes

screening should be aware of these limitations. Where a high risk result is returned, most clinicians will implement preventive therapies and increased surveillance. Where a low risk result is returned, clinicians should be aware of the continuing need for vigilance for late onset pre-eclampsia. Interventional trials currently underway will better inform practice on the role of combined clinical, ultrasound and biochemistry screening for pre-eclampsia.

4.1.1 The role of clinical assessment
Clinical screening for pre-eclampsia includes identifying women at increased risk on the basis of:

(i) Past or family history of pre-eclampsia;
(ii) Presence of an underlying medical disorder such as hypertension, renal disease or diabetes;
(iii) Risk factors in the current pregnancy such as multiple pregnancy;
(iv) Assessment of blood pressure, height and weight.

4.1.2 The role of ultrasound and biochemistry
More recently, the combination of clinical, ultrasound and biochemical screening in early pregnancy has been proposed as a screening test to identify women at increased risk of pre-eclampsia. This screening involves assessment of maternal serum analytes (such as pregnancy associated plasma protein A (PAPP-A) and placental growth factor (Pl GF) together with ultrasound assessment of the uterine artery pulsatility index. Intuitively, this approach is plausible as pre-eclampsia is essentially a placental disorder and angiogenic factors (as measures of placental health) released into the maternal circulation, or increased resistance to uterine artery blood flow (reflecting increased downstream resistance in the placental bed) might be expected to perform well as an early predictor of pre-eclampsia. However, studies assessing these approaches have reported conflicting results. It is important for clinicians and patients to have an understanding of the strengths and limitations of these screening tests, as these may be heavily marketed to pregnant women and their care providers.

4.1.3 How do these tests perform as screening tests for early onset pre-eclampsia?
Arguably, the group where screening would have most to offer is in primigravid women where their risk of pre-eclampsia has not been previously triaged according to outcome of a prior pregnancy. When screening has been confined to these populations, it has been found to have modest predictive ability with high false positive rates. The results have been more encouraging in general maternal populations (nulliparous and multiparous women), with several studies reporting 90-95% sensitivity and 5-10% false positive rate using an algorithm which combines clinical risk factors with uterine artery Doppler and biochemical assessments. Nevertheless, it is important to appreciate that these improvements in detection rates are partly achieved by having multiparous patients in the cohort, who bring very high positive and negative likelihood ratios to the algorithms depending on whether they had pre-eclampsia or not in their first pregnancy. This risk factor is already considered by most clinicians when determining surveillance and treatment in the next pregnancy.

4.1.4 What is the false positive rate?
Proponents of ultrasound and biochemistry screening have proposed a 10% false positive rate (FPR) with combined clinical, biochemistry and ultrasound screening, compared to the originally
published 5% FPR. This means that 10% (100:1000) of the pregnant population will be identified as high risk, for a disease with a prevalence of 3-4:1000. This means 96:1000 will be falsely alarmed that they are at high risk for the serious disease of early onset pre-eclampsia (EOPE), with the potential risks of increased intervention and anxiety.

4.1.5 Have the screening findings been validated in independent populations?
Of some concern, a recent study has been unable to validate the findings of these screening algorithms when applied to an independent validation cohort. Oliveira et al have reported detection rates of between 40 and 50% for Early Onset Pre-eclampsia using the previously published algorithms on a prospectively enrolled cohort of 3422 women. They concluded that first trimester prediction rules for pre-eclampsia (if applied to an external population) underperform in their ability to correctly identify women that develop pre-eclampsia, and that further research is required to determine the factors responsible for the reduction in external validity.

4.1.6 How do these tests perform as screening tests for early vs late onset pre-eclampsia?
While the combined algorithms proposed above may be argued to be effective screening tests for early onset (<34 weeks) pre-eclampsia (a disease with a prevalence of 3-4:1000), it is important to realise that these are not all effective as screening tests for late onset pre-eclampsia (LOPE): after 34 weeks gestation, which has a prevalence approximately 7 times greater (28:1000). The original report of Poon et al reported a sensitivity of just 36% for LOPE at a 5% false positive rate, while Akolekar et al reported a sensitivity of 35% and Scazzocchio of 40% for a 10% false positive rate.

It is important that patients and clinicians are aware that a low risk result does not imply the patient is at low risk of LOPE. LOPE comprises 2/3 of all severe PET, and is associated with a 2-3 fold increase in perinatal mortality rates (PNMR). Accordingly, careful surveillance for this disorder in later pregnancy is still necessary even in women with a low risk result.

<table>
<thead>
<tr>
<th>Recommendation 1</th>
<th>Grade and reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine screening of all pregnant women for pre-eclampsia risk factors is recommended to identify women at increased risk so that they can be offered aspirin, calcium (if diet deficient) and increased surveillance in pregnancy.</td>
<td>Consensus-based recommendation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation 2</th>
<th>Grade and reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>The place of combination ultrasound and serum markers as predictors of later pre-eclampsia awaits further clarification with some studies suggesting this test performs well as a predictor of severe early onset pre-eclampsia, which is rare. It does not perform well as a predictor of (the more common) late onset disease.</td>
<td>Consensus-based recommendation</td>
</tr>
</tbody>
</table>
4.2 Fetal Growth Restriction/Small for Gestational Age

4.2.1 Definitions/diagnosis
Fetal growth restriction (FGR) is defined as the failure of a fetus to reach its growth potential. Small for gestational age (SGA) is defined as an actual birth weight less than the 10th percentile, or estimated fetal weight or an abdominal circumference on ultrasound <10th centile. SGA is often used as a proxy for the identification of FGR, with severe FGR frequently defined as SGA ≤3rd or ≤5th centile. However there is variation in SGA and FGR antenatal diagnosis methods in current practice in Australia and New Zealand, with use of both ultrasound derived estimated fetal weight (EFW) centile charts or birth weight centile charts, and variation in the specific antenatal ultrasound charts used. Recently the INTERGROWTH study has been published; ultrasound charts derived from this prospective multinational observational study may improve the standardisation of diagnosis of SGA.

4.2.2 Clinical significance
Being growth restricted is implicated in half of stillbirths. Perinatal mortality increases with decreasing birth weight centile, with the adjusted perinatal mortality 3 times higher with a birth weight of <5-10th centile and nearly 15 times higher when birth weight is <1st centile. FGR infants also have increased risk of increased neonatal complications, childhood morbidity, and disease in adult life (obesity, type 2 diabetes and cardiovascular disease).

Accurate diagnosis and management of the growth-restricted fetus remains a significant challenge in maternity care. Early identification of at-risk fetuses through a reliable antenatal screening test ideally would allow the implementation of effective preventive measures and timely referral for close monitoring. It would also avoid unnecessary interventions in low-risk fetuses. However, as yet, evidence for the prevention of FGR, or reduction of perinatal mortality in SGA infants remains unclear.

4.2.3 Clinical assessment in predicting FGR/SGA

Fundal height
Clinical examination and measurement of symphysis fundal height (SFH) is unreliable in detecting SGA fetuses with the accuracy of fundal height assessment affected by significant intra- and inter-observer variation. The sensitivity of SFH measurement reported in a cohort of women with term singleton pregnancies was 17.3% for SGA <10 centile and 14.5% for SGA<3 centile with both specificity >90%. Because of the poor detection rate of fundal height for FGR, markers in early pregnancy that might identify pregnancies at risk would be useful as they could allow targeted surveillance.

Maternal risk factors
Clinical assessment provides important information for risk assessment for SGA. All women should be assessed for risk factors for SGA at their booking visit to identify those who need increased monitoring. An approach recommended by the Royal College of Obstetricians and Gynaecologists (RCOG) guidelines is that women with major risk factors should be referred for serial ultrasound from 26-28 weeks gestation for fetal size and wellbeing with umbilical artery Doppler. These major risk factors include previous small for gestational age infants, previous fetal death in-utero, current pre-eclampsia, current significant unexplained antepartum haemorrhage, diabetes mellitus with vascular disease, renal impairment, antiphospholipid antibody syndrome, systemic lupus erythematosus, smoking ≥ 11 cigarettes a day, daily vigorous exercise and maternal age >40

Prenatal Screening for Adverse Pregnancy Outcomes
C-Obs 61
Page |7
years. The RCOG guidelines also suggest that women with three or more minor risk factors, including previous pre-eclampsia, maternal age ≥35 years, daily vigorous exercise, BMI <20 or >35kg/m² should be referred for a uterine artery Doppler at 20-24 weeks, and further ultrasound surveillance should be determined according to the normalcy of this uterine artery Doppler.

Overall, clinical assessment can only be used as a guide in the initial evaluation of pregnant women because the accuracy of these factors alone in predicting SGA is modest. In a large study by Karagiannis et al. (n=32,850) the reported predictive accuracy of maternal risk factors alone with a 5% FPR generated a sensitivity, specificity and likelihood ratio (LR) of 21%, 95% and 4.2, respectively. The detection rate of a screening algorithm using only maternal factors developed in a cohort of 60,626 singleton pregnancies to detect preterm-SGA was found to be 26.1% (95% CI 21.7–31.6) and 37.4% (95% CI 32.1–43.0) based on a false positive rate of 5% and 10%, respectively.

4.2.4 The role of biochemistry as clinical predictors of FGR/SGA

The value of first trimester Down syndrome screening biomarkers in predicting SGA is modest and is not recommended as a screening test purely for the identification of FGR. Although low pregnancy-associated plasma protein A (PAPP-A) <5th centile at time of nuchal translucency screening (<0.4 MoM) has been found to be associated with an increased risk of SGA, the odds ratio (OR) for SGA infant (birth weight <10th centile) and severe SGA (birth weight <3rd centile were 2.7 and 3.7, respectively with the detection rate of SGA being poor at 12% and 16%, respectively. A meta-analysis found that the most accurate predictor for birth weight < 10th centile was PAPP-A <1st centile (0.3MOM); LR+ = 3.50 (2.53,4.82), LR-0.98 (0.97,0.99). For birth weight <5th centile, the most accurate predictor was again PAPP-A <1st centile; LR+ = 4.36 (3.27,5.80), LR-0.97 (0.96,0.98).

Evaluation of a range of biomarkers of angiogenesis, endothelial function and placental proteins measured in serum, blood, urine or amniotic fluid samples at different stages of pregnancy have also been proposed. However, a recent systematic review evaluating 37 various markers found the test performance to be insufficient to recommend use in clinical practice. This included placental growth factor (PIGF), soluble fms-like tyrosine kinase (sFlt-1) and placental protein 13 (PP13). Serum placental protein 13 (PP13) provided the best accuracy results of all biomarkers. Pooled estimates from 4 studies (n=4,456) reported a 22% and 34% sensitivity, 2.3 and 3.6 positive likelihood ratio (LR+) for all and severe FGR, respectively, at a 9% false positive rate (FPR).

Second trimester biomarkers have also been evaluated as markers for growth restriction including the second trimester levels of maternal serum AFP, hCG, uE3 and inhibin A. Again, despite significant statistical associations with various adverse perinatal outcomes, including FGR, the observed diagnostic accuracy was below that of clinical utility.

Poon et al developed a prediction algorithm for SGA requiring delivery before 37 weeks’ gestation (preterm-SGA) based on maternal characteristics, uterine artery pulsatility index, mean arterial pressure, serum pregnancy-associated plasma protein-A and placental growth factor multiple of the median. Using combined screening at 11–13 weeks’ gestation, the detection rates of preterm-SGA increased to 38 and 52% at FPRs of 5 and 10%, respectively.
4.2.5 The role of uterine Doppler ultrasound as clinical predictors of FGR/SGA

Failure of trophoblast invasion of the myometrial spiral arteries in the early stages of pregnancy may lead to persistent high resistance vessels or notching and abnormal flow in the uterine arteries after the 1st trimester. Compared with biochemical biomarkers, use of uterine Doppler ultrasound has demonstrated moderate but slightly better predictive accuracy across different stages of pregnancy. A meta-analysis using first trimester uterine artery Doppler amongst low-risk pregnant women (n=30,454) reported a sensitivity of 39%, FPR of 7% and a LR+ of 5.7 in predicting early-onset FGR. Sensitivity, FPR and PLR for FGR at any gestational age were 15%, 7% and 2.3, respectively. 23 Fetal growth restriction in low-risk patients was best predicted in the second trimester by an increased pulsatility index with notching (positive likelihood ratio 9.1, 95% CI 5.0–16.7; negative likelihood ratio 0.89, 95% CI 0.85–0.93). 24

4.2.6 Conclusion and suggestions for management

The quest for screening tests to effectively identify pregnancies at-risk of FGR has attracted increasing interest, due to the potential benefits of early and close monitoring of women. However, to date the predictive accuracy of biochemical biomarkers and ultrasound techniques in detecting fetuses at-risk of growth restriction/small for gestational age has not provided auspicious results. The evaluation of a combination of biomarkers, Doppler ultrasound and maternal clinical risk factors in first trimester of pregnancy has provided better results; future research is necessary to establish the predictive accuracy and cost effectiveness of these tests.

Recommendation 3

The predictive accuracy of biochemical biomarkers and ultrasound techniques in detecting fetuses at-risk of growth restriction/small for gestational age has not provided auspicious results. The evaluation of a combination of certain biomarkers, Doppler ultrasound and maternal clinical risk factors in first trimester of pregnancy provides better results; further research will evaluate the predictive ability and cost effectiveness of these tests.

<table>
<thead>
<tr>
<th>Grade and reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consensus-based recommendation</td>
</tr>
</tbody>
</table>
4.3 Preterm birth

4.3.1 The importance of preterm birth
15 million babies are born preterm every year and over 1 million children die each year due to complications of preterm birth. Many survivors of preterm birth have disabilities including cerebral palsy, learning difficulties and visual and hearing problems. The preterm birth rate in Australia is approximately 7% and has been stable at this level for a number of years.

Nearly half of preterm births are idiopathic after spontaneous onset of labour, but 30% are associated with preterm rupture of membranes (PROM) and 15–20% to medical or elective preterm deliveries. Early detection of high-risk pregnancies is an important priority for maternal and infant healthcare to ensure timely introduction of close monitoring and preventive treatment.

4.3.2 Risk factors for Preterm Birth
Risk factors for spontaneous preterm birth include a history of preterm birth, multiple pregnancy and a short cervical length in the mid-trimester. Other risk factors include mid-trimester pregnancy loss, uterine anomalies, smoking, low body mass index (BMI) and a history of a previous cone biopsy of the cervix. Women should be assessed for the presence of risk factors at their initial assessment, in order to stratify women to the appropriate level of obstetric care. Modifiable risk factors such as smoking or sub-optimal BMI should be addressed prior to pregnancy.

Recent interventions such as progesterone therapy have been shown to be effective in reducing the risk of preterm birth in selected high risk women, notably those with a previous preterm birth, and women with a short cervical length detected in the mid trimester. Given the benefits of screening and treatment, a history of a previous preterm birth should identify a woman as high risk, and transvaginal cervical length measurement should be offered. The addition of quantitative fetal fibronectin may assist in further refining the risk of preterm birth among high risk women with a short cervical length.

4.3.3 The Role of ultrasound Transvaginal Cervical Length as a Predictor of Spontaneous Preterm Birth
ASUM (Australasian Society for Ultrasound in Medicine) have recommended that all women have a cervical length measurement at the mid-trimester morphology ultrasound. The most recent revision of the ASUM mid-trimester ultrasound guidelines in September 2014 recommends that the cervical length be measured and it should be noted to be open or closed. The guideline is not proscriptive about the method of sonographic measurement, but a transvaginal measurement is more accurate in determining risk of preterm birth. For further guidance on the use of cervical length in low and high risk women, and the role of progesterone to reduce the risk of preterm birth, please refer to the College Statements C- Obs 27 and C-Obs 29-b.

4.3.4 The role of biochemical biomarkers as predictors of spontaneous preterm birth in asymptomatic women Fetal fibronectin has an established role in women presenting with threatened preterm labour, both alone and in combination with transvaginal cervical length measurement. There are a number of biochemical biomarkers other than Fetal Fibronectin (fFN) measured in blood, amniotic and cervicovaginal fluid that have been investigated as potential early predictors of preterm birth among asymptomatic women. A systematic review summarised the results of studies on biomarkers and reported that no single biomarker in asymptomatic women with singleton pregnancies, produce acceptable predictive accuracy results suitable to use in clinical practice.
4.3.5 Conclusion and Recommendations

Recommendation 4

All women should be assessed for risk factors for preterm birth. Women with a past history of spontaneous preterm birth should be offered progesterone to reduce their risk of recurrent preterm birth. For further guidance, please refer to College Statements *Progesterone Support of the Luteal Phase and Early Pregnancy (C-Obs 29a)* and *Progesterone: Use in the Second Trimester and Third Trimester of Pregnancy (C-Obs 29b)*.

**Grade and reference**

Consensus-based recommendation

Recommendation 5

Women with risk factors for spontaneous preterm birth benefit from serial assessment of cervical length by transvaginal ultrasound to permit interventions to reduce their risk of preterm birth.

**Grade and reference**

Consensus-based recommendation

Recommendation 6

All women should have an assessment of the cervical length at the mid-trimester ultrasound, given the potential benefit of treatment options (such as progesterone and cervical cerclage) for a sonographically short cervical length in reducing the risk of preterm birth. For further guidance, please refer to College Statements *Cervical Length in Pregnancy, Measurement of (C-Obs 27)* and *Progesterone: Use in the Second Trimester and Third Trimester of Pregnancy (C-Obs 29b)*.

**Grade and reference**

Consensus-based recommendation

Recommendation 7

Fetal fibronectin has value in identifying women with threatened preterm labour at high risk of preterm birth. To date, there are no other biomarkers in early pregnancy with sufficient accuracy for predicting later preterm birth.

**Grade and reference**

Consensus-based recommendation

5. Conclusion

Pre-eclampsia, preterm birth and fetal growth restriction are important contributors to adverse perinatal outcome. Identification of high risk women in early pregnancy is optimal since it facilitates timely initiation of preventive treatment and an opportunity to tailor antenatal care and ongoing surveillance. Women may be stratified as low or high risk on the basis of clinical history alone or in combination with ultrasound or biomarkers. Clinicians should be aware of the relevant sensitivity, FPR and positive/negative likelihood ratios for these advanced screening tests, both to determine the suitability of their patient for the test and to assist with interpretation of a positive or negative finding.
6. References


7. Links to other College statements
RANZCOG/HGSA Prenatal Screening and Diagnosis of Chromosomal and Genetic Abnormalities in the Fetus in Pregnancy (C-Obs 59)
RANZCOG/HGSA Prenatal Assessment of Fetal Structural Abnormalities (C-Obs 60)
Mid-trimester fetal morphology ultrasound screening (C-Obs 57)
Prenatal Screening for Fetal Abnormalities (C-Obs 35)
Pre-pregnancy Counselling (C-Obs 3a)
Routine Antenatal Assessment in the Absence of Pregnancy Complications (C-Obs 3(b))
Measurement of Cervical Length in Pregnancy (C-Obs 27)
Progesterone Support of the Luteal Phase and Early Pregnancy (C-Obs 29a)
Progesterone: Use in the Second Trimester and Third Trimester of Pregnancy (C-Obs 29b)
Position Statement on the Appropriate Use of Ultrasound (C-Gen 10)
6. Patient information

A range of RANZCOG Patient Information Pamphlets can be ordered via:
Appendices

Appendix A Women’s Health Committee Membership

<table>
<thead>
<tr>
<th>Name</th>
<th>Position on Committee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associate Professor Stephen Robson</td>
<td>Chair and Board Member</td>
</tr>
<tr>
<td>Dr James Harvey</td>
<td>Deputy Chair and Councillor</td>
</tr>
<tr>
<td>Associate Professor Anusch Yazdani</td>
<td>Member and Councillor</td>
</tr>
<tr>
<td>Associate Professor Ian Pettigrew</td>
<td>Member and Councillor</td>
</tr>
<tr>
<td>Dr Ian Page</td>
<td>Member and Councillor</td>
</tr>
<tr>
<td>Professor Yee Leung</td>
<td>Member of EAC Committee</td>
</tr>
<tr>
<td>Professor Sue Walker</td>
<td>General Member</td>
</tr>
<tr>
<td>Dr Lisa Hui</td>
<td>General Member</td>
</tr>
<tr>
<td>Dr Joseph Sgroi</td>
<td>General Member</td>
</tr>
<tr>
<td>Dr Marilyn Clarke</td>
<td>General Member</td>
</tr>
<tr>
<td>Dr Donald Clark</td>
<td>General Member</td>
</tr>
<tr>
<td>Associate Professor Janet Vaughan</td>
<td>General Member</td>
</tr>
<tr>
<td>Dr Benjamin Bopp</td>
<td>General Member</td>
</tr>
<tr>
<td>Associate Professor Kirsten Black</td>
<td>General Member</td>
</tr>
<tr>
<td>Dr Jacqueline Boyle</td>
<td>Chair of the ATSIWHC</td>
</tr>
<tr>
<td>Dr Martin Byrne</td>
<td>GPOAC representative</td>
</tr>
<tr>
<td>Ms Catherine Whitby</td>
<td>Community representative</td>
</tr>
<tr>
<td>Ms Sherryn Elworthy</td>
<td>Midwifery representative</td>
</tr>
<tr>
<td>Dr Nicola Denton</td>
<td>Trainee representative</td>
</tr>
</tbody>
</table>

Appendix B Contributing Authors

The Women’s Health Committee acknowledges the contribution of Dr Antonia Shand, Dr Margaret Harpham and Dr Francisco Schneuer to this statement.
Appendix C Overview of the Development and Review Process for this Statement

i. Steps in developing and updating this statement

This statement was originally developed during 2015. The writing group and Women’s Health Committee carried out the following steps in reviewing this statement:

- Declarations of interest were sought from all members prior to reviewing this statement.
- Structured clinical questions were developed and agreed upon by the writing group and Women’s Health Committee.
- An updated literature search to answer the clinical questions was undertaken.
- The writing group were asked to draft specific questions of relevance to their area of expertise.
- At the July 2015 committee meeting, the draft was reviewed by Women’s Health Committee and was recommended to RANZCOG Board and Council.

ii. Declaration of interest process and management

Declaring interests is essential in order to prevent any potential conflict between the private interests of members, and their duties as part of the Women’s Health Committee.

A declaration of interest form specific to guidelines and statements was developed by RANZCOG and approved by the RANZCOG Board in September 2012. The Women’s Health Committee and writing group members were required to declare their relevant interests in writing on this form prior to participating in the review of this statement.

Members were required to update their information as soon as they become aware of any changes to their interests and there was also a standing agenda item at each meeting where declarations of interest were called for and recorded as part of the meeting minutes.

There were no significant real or perceived conflicts of interest that required management during the process of updating this statement.

iii. Grading of recommendations

Each recommendation in this College statement is given an overall grade as per the table below, based on the National Health and Medical Research Council (NHMRC) Levels of Evidence and Grades of Recommendations for Developers of Guidelines. Where no robust evidence was available but there was sufficient consensus within the HGSA/RANZCOG Joint Committee on Prenatal Diagnosis and Screening Committee, consensus-based recommendations were developed or existing ones updated (and are identifiable as such). Consensus-based recommendations were agreed to by the entire Committee. Good Practice Notes are highlighted throughout and provide practical guidance to facilitate implementation. These were also developed through consensus of the entire Committee.
### Recommendation category

<table>
<thead>
<tr>
<th>Description</th>
<th>Evidence-based</th>
<th>Consensus-based</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body of evidence can be trusted to guide practice</td>
<td><strong>A</strong></td>
<td>Recommendation based on clinical opinion and expertise as insufficient evidence available</td>
</tr>
<tr>
<td>Body of evidence can be trusted to guide practice in most situations</td>
<td><strong>B</strong></td>
<td></td>
</tr>
<tr>
<td>Body of evidence provides some support for recommendation(s) but care should be taken in its application</td>
<td><strong>C</strong></td>
<td></td>
</tr>
<tr>
<td>The body of evidence is weak and the recommendation must be applied with caution</td>
<td><strong>D</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Good Practice Note**

Practical advice and information based on clinical opinion and expertise

---

**Appendix D Full Disclaimer**

This information is intended to provide general advice to practitioners, and should not be relied on as a substitute for proper assessment with respect to the particular circumstances of each case and the needs of any patient.

This information has been prepared having regard to general circumstances. It is the responsibility of each practitioner to have regard to the particular circumstances of each case. Clinical management should be responsive to the needs of the individual patient and the particular circumstances of each case.

This information has been prepared having regard to the information available at the time of its preparation, and each practitioner should have regard to relevant information, research or material which may have been published or become available subsequently.

Whilst the College endeavours to ensure that information is accurate and current at the time of preparation, it takes no responsibility for matters arising from changed circumstances or information or material that may have become subsequently available.