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A Pragmatic Approach to the Prevention of Preterm Birth

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Introduction

Preterm birth (PTB) -delivery before 37 weeks of gestation- occurs in ~8% of Canadian pregnancies, a rate that has remained stable for >20 years.[1] Prematurity remains the leading cause of neonatal mortality- especially at the extreme of viability: 22–26 weeks gestation. Children born prematurely have increased rates of cerebral palsy, global neurodevelopmental impairment, learning disabilities, deafness, vision impairment and behavioural diagnoses.[1] Hospital length of stay and re-admission rates in the first year of life are higher in babies born preterm.[1] The family impact is immeasurable in the domains of mental health diagnoses, financial health, and disordered social interactions.[1] Prematurity has a longitudinal impact on reproductive and public health with an increased risk of occurrence in subsequent pregnancies.[1]

The phenotype of PTB can be described as spontaneous (SPTB) versus iatrogenic or defined by clinical presentation: labor, antepartum hemorrhage, premature ruptured membranes, hypertensive disorder, cervical insufficiency.[2] PTB is best appreciated as a syndrome attributed to one or more contributing underlying pathologies (intrauterine infection, abnormal placentation), one or more identified risk factors (smoking, malnutrition, short interpregnancy interval) and most commonly one or more unknown "idiopathic" influence(s).[2] PTB must be considered a heterogenous condition. It is this heterogeneity which drives frustration in the prevention of PTB. No one intervention has been demonstrated to universally reduce the risk or prevent PTB for all comers. As such, a pragmatic population and individual based strategy for PTB prevention takes on a two-pronged approach. "Primary prevention" is targeted at all pregnant or future pregnant individuals to optimize the gestational age at delivery and "secondary prevention" is targeted at an at-risk population based on maternal health/risk factors, obstetrical history and/or clinical risk factors identified through the course of the pregnancy. The hypothesis underlying this tactic is that the synergistic effect of a multi-modal approach leading to an individualized strategy will best optimize pregnancy outcome: decrease the risk of PTB or at minimum, prolong gestational length.

Prevention starts with pre-pregnancy counselling focussed on maternal health, and lifestyle optimization. Contraceptive counselling and access to safe, low-cost birth control decreases the rate of adolescent pregnancy and its associated risk of PTB.[3,4] Effective post partum contraceptive counselling is important as short

inter-pregnancy interval (<6 months) increases PTB risk (OR 1.45).[3,4] This can be challenging when counselling a patient following a PTB with neonatal death or a previable loss as there is a sense of urgency for the next pregnancy. Pre-pregnancy weight management is important; BMI <20 is associated with increased risk (OR 1.32).[3,4] Obesity (BMI >25) is linked to pregnancy complications associated with PTB including hypertensive disorders, poor fetal growth, congenital malformations, and diabetes.[3,4] Optimizing maternal health conditions such as hypertension, diabetes and anemia improves the risk of PTB. Smoking and recreation drug use doubles the rate of prematurity; smoking cessation, including the use of a substitute nicotine patch, has a well studied benefit.[3,4] As multiple gestations have a mean gestational age of <37 weeks, single embryo transfer at the time of IVF is an important consideration for optimizing outcome. Screening for and managing mental health diagnoses (especially anxiety and depression) and intimate partner violence contribute to risk reduction.[3,4]

Early pregnancy care is critical; it is well recognized in both developing and developed countries that limited, or no antenatal care is associated with PTB. "Mid-wife led continuity of antenatal care models" are associated with reduced rates of PTB, stressing the importance of supportive care for the health and well-being of women through pregnancy.[4] Specialized PTB clinics providing dedicated care for women at risk of PTB have shown a risk reduction and are mechanism to address the emotional, psychosocial stressors of an "at risk pregnancy".[4] Lifestyle and nutrition guidance contribute to pregnancy outcome. A "healthy" dietary pattern higher in fruits, vegetables, legumes, and whole grains is associated with a lower risk of PTB. Micronutrient supplementation with vitamin D, Zinc, DHEA and calcium are associated with pregnancy prolongation and reduction of early PTB.[4] Periodontal disease is associated with prematurity; a dental exam early in pregnancy may be provide benefit on an individual level.[3,4] Screening and treatment for lower genital tract infections (syphilis and vaginal candidiasis) and asymptomatic bacteriuria have well established impact on risk reduction.[3,4] Bacterial vaginosis (BV) is strongly associated with SPTB; diagnosis and management of BV should be part of routine antenatal care. Genital tract colonization with *Ureaplasma* species is associated with PTB and *Ureaplasma* is a commonly isolated bacteria from the amniotic fluid and placenta of patients delivering preterm.[5] There is insufficient evidence to determine if universal screening and treatment of *Ureaplasma* has a beneficial impact on PTB prevention; however, the use of macrolide antibiotics targeted at *Ureaplasma* in pregnancy is safe.[5] Based on an individualized approach focussed on risk factor modification, screening and treatment for *Ureaplasma* may be of benefit, particularly in patients with a history of infection mediated PTB. The use of probiotic(s) to reduce the rates of vaginal infections, in particular BV, is recommended outside of pregnancy; there no evidence that taking probiotics during pregnancy decreases the risk of PTB but could be useful on the individual level for risk reduction.[4,6]

Secondary prevention is targeted at individuals at risk of PTB; these targeted interventions include aspirin (ASA), vaginal progesterone (VP), and cervical cerclage.[4,7,11,12,13] The Aspirin for Evidence-Based Preeclampsia Prevention trial demonstrated that ASA has a significant risk reduction for early onset pre-eclampsia (PET) (<34w gestation) with or without fetal growth restriction. At risk patients can be identified by demographics factors: maternal age >30, BMI >35, IVF achieved pregnancy, twin pregnancy, history of PET and maternal health conditions including chronic hypertension, diabetes, lupus and anti-phospholipid antibody syndrome.[7] The Fetal Medicine Foundation provides an easily accessible online tool for PET prediction at 11–14 weeks' gestation using maternal characteristics, medical and obstetric history, mean arterial blood pressure, uterine artery Doppler ultrasound and serum biomarkers (pregnancy associated placenta protein A and/or placenta like growth factor) which will identify a greater number of patients at risk compared with risk-factor-based screening alone.[7,8] A daily dose of ASA, ideally 150 mg, at night, initiated before 16 weeks' gestation, and maintained until 36 weeks' gestation or birth demonstrates a dramatic decrease in the rate of early onset PET. Although one small study of patients at risk for SPTB did not show benefit of ASA, it should be noted that placenta pathological findings associated with PET (fetal and maternal vascular mal-perfusion, perivillous fibrin deposition, immature, avascular villi) are also associated with SPTB.[9] Based on the beneficial effect of ASA for PET prevention driven by these pathological findings, it is reasonable to

recommend ASA supplement in patients with these placental findings in the subsequent pregnancy.

Natural micronized vaginal progesterone (VP) supplement and cerclage have been hailed as the gold standard interventions to prevent SPTB in at risk individuals.[4,10,11,12,13] The mechanism(s) by which VP prevents SPTB are not clear but may involve the molecular pathways of premature cervical ripening, inhibition of uterine contractility and/or an anti-inflammatory effect on the labor cascade. A comprehensive individual patient data (IPD) meta-analysis makes the following recommendations regarding the use of VP.[10] In patients with a transvaginal sonographic short cervix (<25 mm) identified mid-trimester (18–24 weeks gestation), VP (100–200 mg) continued until term significantly decreased the risk of PTB at <36w gestation and the rate adverse neonatal outcomes associated with prematurity: RDS, composite neonatal morbidity and mortality, low birth weight and NICU admission.[10] In patients with a twin gestation and mid-gestation cervix length <25mm, VP reduces the risk of PTB occurring at <34 weeks gestation and the associated risk of perinatal morbidity.[10] There is no evidence to support VP use in twin or higher-order multifetal gestations in the absence of a short cervix.[4,10]

The role for VP in patients with history of SPTB is controversial. Many small studies strongly support the use of VP in these patients. However, the IPD meta-analysis, with an adjustment for small-study effects, demonstrated a nonsignificant effect of VP in this population.[10] Alternatively, a systematic review and meta-analysis demonstrated an effect of VP on PTB <37 weeks (RR 0.78).[4,11] In addition, no adverse maternal and/or neonatal effects were reported. Given the multifactorial and not well understood etiology of SPTB, the potential benefit on an individual level and its safety profile, the use VP for patients with a history of SPTB should be recommended and is supported by clinical practice guidelines from governing obstetrical societies.

A cervical cerclage, which offers mechanical support to the cervix by placing a suture around the cervix, assumes that such re-enforcement will reduce the rate of SPTB.[4,12,13] A cerclage has also been described as a rescue, emergency surgical intervention to close the cervical os in a patient presenting with an open cervix. A cerclage placed based on a history of SPTB alone (prophylactic) has not been found to be of any benefit except for a modest risk reduction in the context of 3 or more second trimester losses.[4,12] A cerclage placed because of a short mid-gestation cervical length (<25mm) regardless of obstetrical history, significantly reduced the risk of PTB <37 weeks (RR 0.72).[4,12,13] This effectiveness of a cerclage, prophylactic or indicated by cervical length, in twin gestation and higher order multiple gestation has not been proven beneficial and thus should not be routinely recommended.[4,12] A rescue cerclage does prolong gestation and decrease the rate of SPTB, however, there is significant infectious morbidity associated with such intervention and should be used with caution and informed counselling.[4,12,13] It should be noted that a cerclage is a much more invasive and costly intervention compared with VP. A cerclage can impart residual trauma and laceration to the cervix impacting its mechanical function in a subsequent pregnancy. A cerclage does not consider or treat the recognized pathologies triggering a PTB: intrauterine infection and abnormal placentation. A short and/or open cervix in the current or prior pregnancy is not solely attributed to an impaired ability of the ultrastructure of the cervix to withstand the deformative pressures of the increasing uterine muscle bulk and the uterine contents: placenta, amniotic fluid and fetus. Premature cervical ripening is an under appreciated contributor to the shortening of a cervix. In addition, a short cervix may have a secondarily acquired ascending intra-uterine infection, which would contribute to the failure of this intervention. It would be naïve to assume a cerclage alone would be universally effective as is often suggested at the time of a PTB or requested by a patient seeking care after loss.

Unfortunately, there are no studies comparing VP head-to-head with cerclage or studies with VP+cerclage versus placebo. It is intuitive to combine such interventions based on individualized multi-modal approach to a multifactorial diagnosis, recognizing the risk associated with each intervention and counselling to ensure an understanding that no one intervention has been shown to 100% eliminate the chance of a PTB. However, it should be recognized that both VP and cerclage have protective benefit for individuals with a mid-gestation short cervix providing strong rationale for the universal screening of cervix length for all pregnant individuals as a population-based strategy for SPTB prevention. Interventions such as a vaginal pessary, bed rest, home uterine monitoring and the use of tocolytic agents (including VP

in this setting) have no impact on the rate of SPTB and should not part of routine or targeted pregnancy care.

Conclusion

In summary, PTB is a heterogenous condition requiring both population based and individualized prevention strategies. Healthy lifestyle, nutrient supplements, reproductive counselling, psycho-social support, packages of antenatal care, treatment of genital tract infections are population-based strategies for risk reduction.[4,13] Risk factor screening and mid-gestation cervical length assessment to identify an at-risk population for whom the use of VP, aspirin and/or cerclage has proven benefit in the prevention of PTB.[4,10,11,12,13] The national and international rate of PTB has not improved over the past 20 years, proving that these interventions alone are insufficient at eliminating and/or reducing PTB. An improved understanding of the etiology of PTB to drive prevention care is an obstetrical imperative.

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Financial Disclosures

None declared.

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