

## Changing Preterm Birth in Delaware

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### Introduction & Epidemiology

Preterm delivery (delivery prior to 37 weeks 0/7 days gestation) remains the dominant cause of neonatal morbidity and mortality throughout the world.<sup>1-3</sup>

In the state of Delaware the rate of preterm birth was noted to be 10.1% in 2016, a slight increase from 2015.<sup>4</sup> Fortunately, the majority (70%) of preterm births occur in the late preterm birth period, between 34 0/7 weeks and 36 6/7 weeks, where the outcomes are generally more favorable.<sup>5</sup> Though preterm births prior to 34 weeks are less common, the most neonatal deaths result from children born before 34 weeks. Likewise significant differences exist between different ethnic groups with African American women having an 11.8% rate of preterm birth compared to Hispanics (7.9%) and Caucasians (9.0%).<sup>4</sup>

In addition to the individual burdens of preterm birth, significant financial burdens result from prematurity. Recent estimates of direct inpatient costs attributable to prematurity are largely unavailable; however, in 2005 the direct medical costs for preterm infants born in the United States were noted to exceed 26.2\$ billion dollars.<sup>6</sup> Children born at earlier gestational ages are noted to have proportionally higher health care costs than those born later in pregnancy. This estimate of cost does not reflect the longitudinal medical costs beyond the birth hospitalization which are known to be significantly higher than children born at term.

Children born prematurely are also at an increased risk for long term medical complications such as respiratory, gastrointestinal, cardiovascular, and metabolic disorders.<sup>7,8</sup> Premature children born are also known to have a variety of learning delays including lower IQ's, difficulty with language acquisition and are more likely to have neurobehavioral challenges.<sup>9-11</sup> Overall, approximately 50% of pediatric neurodevelopmental disorders are attributed to prematurity.<sup>12</sup>

### Biology of Prematurity

Increasingly preterm birth has become recognized as an outcome of a series of antecedent causes with a common final pathway.<sup>13</sup> It should be remembered that approximately 40% of prematurity is due to iatrogenic preterm birth, which is mostly the result of preeclampsia and fetal growth restriction. The remaining 60% of prematurity is the result of spontaneous preterm birth. Most researchers are increasingly viewing spontaneous preterm birth as being the result of the following causes: decidual hemorrhage, inflammation/infection, uterine distention, maternal stress, cervical insufficiency, preterm premature rupture of the membranes, maternal comorbidities, familial factors and premature activation of the fetal hypothalamic-pituitary-adrenal (HPA) axis.<sup>14</sup> Spontaneous preterm births prior to 28 weeks (the largest cause of mortality) are largely driven by three predominant causes: infection/inflammation, decidual hemorrhage and cervical insufficiency. Due to this complexity, effective prevention and treatment of preterm birth may require pathway specific treatments and that a solitary treatment approach may not exist.

## Iatrogenic Prematurity

As 40% of preterm births are iatrogenic, assuring that providers are evidenced based in their approach to elective preterm delivery may be a great opportunity. In an examination of iatrogenic late preterm births (34 to 37 weeks), Gyamfi, et al. found that 56.7% of iatrogenic late preterm births were not supported by nationally published guidelines though all cases of iatrogenic preterm birth had a reason for delivery<sup>15</sup>. Both the publication of national guidelines on the timing of iatrogenic delivery to specific obstetrical conditions<sup>16</sup> and public reporting of elective deliveries prior to 39 weeks have resulted in a significant decline in iatrogenic prematurity.<sup>17</sup>

Nonetheless, iatrogenic preterm delivery are mostly due to preeclampsia and fetal growth restriction and strategies to mitigate these causes are increasingly being employed. Recognizing that these diseases are vascularly mediated and begin early in pregnancy, several professional organizations have recommended the use of low dose aspirin for the prevention of preeclampsia in at-risk women early in pregnancy (13 weeks).<sup>18,19</sup>

Meta-analyses of low dose aspirin have suggested a 20% reduction in the risk of preeclampsia and similarly a lowering of the risk of fetal growth restriction.<sup>20,21</sup>

Pravastatin which has long been used to treat adult vascular disease may play an important role<sup>22</sup> to prevent preeclampsia to women who are deemed at risk for this condition. Trials in women at high risk for recurrent preeclampsia are currently being planned.

## Prediction of preterm birth

Accurate prediction of preterm birth would allow providers to identify treat women at risk in a much more systematic way. Historical or clinical risk factors have long been utilized to identify women at risk for preterm birth. Socio-economic status, ethnicity (particularly African-American race), geographic location, and maternal stress have been established as risk factors for preterm birth; though their ability to identify women who will deliver prematurely are extremely limited.<sup>23,24</sup>

The most predictive factor for subsequent preterm birth in a singleton gestation is having had a prior preterm birth, which carries an approximate risk of 30% in a subsequent pregnancy. For African-American women, those with earlier preterm births and those with multiple prior preterm births, a history of a prior preterm birth is an even stronger risk factor.<sup>25</sup>

Researchers have begun to look for other markers for preterm birth. Transvaginal cervical ultrasound measurement of the cervical length has been a frequent subject of investigation.<sup>26</sup> Two authors have suggested that universal transvaginal cervical length screening when coupled with treatment with vaginal progesterone is a cost effective strategy.<sup>27,28</sup> Nonetheless, full implementation of such a strategy would only result in a small decrease in the overall rate of preterm birth. Moreover, a recent prospective study of nulliparous women demonstrated that only a minority (AUC= 0.58) of women who deliver prematurely will be detected through cervical length screening; limiting its usefulness as a strategy.<sup>29</sup>

Another marker that has garnered research interest is fetal fibronectin, an anchor protein from the maternal decidua to the fetal chorion<sup>30</sup>. Though fetal fibronectin has been accepted as a useful test (high negative predictive value) in women who present with symptoms of preterm labor from 24 to 34 weeks, the utility of this test to identify asymptomatic women who will deliver

prematurely remains in question. The results of several investigations have been mixed and a recent large prospective trial has suggested that the predictive ability of fibronectin is poor.<sup>30</sup>

Recognizing that proteomic expression in the placenta may portend preterm birth, researchers have become interested in the role of proteomics and preterm birth. Saade and colleagues recently examined both proteins associated with pregnancy and novel discovery of random proteins to determine their predictive ability to identify women at risk for preterm birth amongst 5501 women.<sup>31</sup> The group identified and subsequently developed an FDA approved blood test obtained at 19 to 21 weeks that accurately identifies women who will deliver prematurely. This test has demonstrated moderate sensitivity and specificity for preterm birth <37 weeks (AUC=0.75) but had high sensitivity at predicting preterm delivery <35weeks (AUC=0.92). Though promising, studies coupling the use of this test with treatment will be required to demonstrate the utility of such a test. Similarly, the University of California San Francisco has announced the development of a test that utilizes a mixture of clinical information and blood analytes that claims to prospectively identify 80% of preterm births.<sup>12</sup>

## Treatment

Equally important to identifying women at risk for preterm birth, is the development of effective treatment strategies. Three studies of giving exogenous progesterone to women with risk factors for preterm birth have suggested benefit. The Maternal Fetal Medicine Units randomized 434 women with a prior history of preterm birth begun between 16 to 20 weeks to either 250mg of 17 alpha-hydroxyprogesterone caproate (17-OHPC) on a weekly basis or an identical placebo.<sup>32</sup> Women who received 17 OHPC were approximately a third less likely to deliver prior to 34 and 37 weeks compared to women who received a placebo. Hassan and colleagues randomized women with a cervical length between 10-20mm<sup>33</sup> and Da Fonseca randomized women with a cervical length <15mm to vaginal progesterone or an identical placebo and both showed a decrease in preterm birth prior to 34 weeks<sup>34</sup>. Though promising, multiple other trials using different formulations or risk factors to preterm birth<sup>35,36</sup> have failed to demonstrate any benefit to antenatal progesterone.

Another medical approach is the use of low dose aspirin. Studies of LDA to prevent preeclampsia have enrolled greater than 43,000 women for the indication of preventing preeclampsia.<sup>37</sup> These studies have suggested a moderate reduction in the risk of preterm birth (AOR 0.8). This effect may be amplified by beginning LDA before 16 weeks and using higher doses (100mg to 150mg).<sup>38</sup> Other analyses of primary studies have suggested a trend towards lower rates of prematurity in women taking early low-dose aspirin. These studies have lacked significant power to firmly establish the potential role of LDA in the prevention of preterm birth.<sup>39</sup>

Currently a trial of nearly 12,000 first time mothers in low/middle Income countries has been undertaken and recruitment will be completed in June of 2018.<sup>40</sup>

Interest in pessaries to support the cervix was recently piqued by the Spanish Pesario Cervical para Evitar Prematuridad (PECEP) trial.<sup>41</sup> In this trial, 385 women with a singleton pregnancy with a short cervix by ultrasound were randomized to an Arabin pessary or usual care. Those who received a pessary (N=192) were less likely to deliver before 34 weeks (OR 0.18, 95% CI 0.08-0.37; p<0.0001). Similar outcomes were seen in an Italian trial of 300 women.<sup>42</sup> In contrast, an international trial of 942 women who had a short cervix and were randomized to

either a pessary or placebo and found no difference in the rate of women delivering before 34 weeks.<sup>43</sup> This trial differed from the (PECEP) trial in that women received progesterone for a cervical length under 15mm and 24.5% of women had removal of the pessary.

## Social Determinants

Finally it should be remembered that beyond the medical issues of preterm birth, the social determinants of health have long been chronicled to have profound impacts on health outcomes and preterm birth. Being of African-American race has long been documented to be a risk factor for preterm birth<sup>44</sup> and outcomes worse amongst women living in poverty. Compounding the issue is that living in poverty may further compound the social and developmental growth of children born prematurely.<sup>44</sup> Likewise, women of reproductive age are increasingly ethnically diverse and are at risk of living in poverty within the current demographic shifts that occurring within the US.<sup>45</sup> To address this issue, ACOG and other professional organizations have recommended that routine screening be performed to address inequities in reproductive health.<sup>46</sup> Likewise, ACOG notes that opportunities to improve patient center outcomes can be done through medical-legal partnerships, liaisons with community based social needs programs, interpreter services and coalitions that can address transportation and logistical challenges. Further research demonstrating improved outcomes from strategies addressing these concerns are wanting; however, it must be acknowledged that the social determinants of health are integral if we are to engage in the issue of prematurity.

## Conclusion

Despite years of stagnation and a failure to improve the rates of preterm birth within Delaware, a deeper scientific understanding of the underlying biology provides a potential road map for novel diagnostic studies and therapeutic options. Current studies are underway, potentially offering new hope to the families and children.

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