2. Invited Commentary by Dr Anne Twomey: The impact on prematurity on our perinatal mortality rate

The NPEC has now published its seventh annual report on perinatal mortality in Ireland. The fundamental aim of this yearly audit is to improve the care of mothers and babies in Ireland. Each year in Ireland, approximately 400 babies are stillbirth or die within the first week. The loss of a baby, whether a stillbirth or a neonatal death, is a devastating outcome for all concerned and has lasting effects on parents, families and healthcare professionals. By providing key epidemiological data and monitoring adverse outcomes, this annual report aspires to drive improvements in perinatal care. Previous commentaries have focused on stillbirth, deaths due to congenital anomalies and intrapartum deaths. However, one area that has not received much attention has been the impact of preterm birth (PTB) on our national perinatal mortality rate (PMR).

To place the impact of prematurity in context, it is worthwhile considering the following figures which are presented in this year's report. In 2017, there were 345 deaths classified as perinatal deaths. Of these, 235 were stillbirths (>500g and/or ≥24wks gestation) and 110 were deaths of liveborn infants within the first 7 days of life. Of the 110 early neonatal deaths, 61 cases were due to a major congenital anomaly. Of the remaining 49 cases occurring in normally formed infants, a total of 36 cases died from conditions directly related to prematurity; 24 died of respiratory conditions, four died of necrotising enterocolitis (NEC), six died of Intraventricular/periventricular haemorrhage (IVH) and two were pre-viable. In summary, of a total of 110 early neonatal deaths in normally formed infants, 36 (32.7%) cases were directly attributable to preterm birth. From a neonatologist's perspective, these numbers do not reflect the true impact of preterm birth. If late neonatal deaths (ie those deaths occurring between 7-28 days of life) are included, another 10 of 35 deaths occurring in normally formed infants in 2017 were as a direct consequence of prematurity. Lastly, based on a legal definition used by the NPEC that excludes liveborn infants <24wks gestation and <500g from our perinatal mortality rate figures, a further 38 normally formed infants died in the first few days of life as a direct consequence of preterm birth.

For this year's commentary, we have decided to focus on the subset of women who experience a perinatal death of a normally formed liveborn infant weighing ≤1500g. We wanted to determine if these women differed from other women who had experienced a perinatal loss. Our aim was to identify any epidemiological factors and/or maternal or foetal risk factors that could ultimately lead to improvements in care. For the purpose of this study, all liveborn infants ≥401g and ≤1500g and/or ≥22wks and ≤29wks gestation (please see eligibility criteria for the Very Low Birth Weight (VLBW) Infants in the Republic of Ireland Annual Report) were included in the study population if the infant died within the first 28 days of life. Infants with major congenital anomaly were excluded. The comparison group was all other cases of perinatal deaths in the first 28 days not related to a congenital anomaly. Data from the previous NPEC audits for the years 2011-2016 were included. Many neonatologists may query why we did not focus exclusively on all the VLBW infants who were born in Ireland during the same time period (ie the cohort of infants in the VLBW Infants in the Republic of Ireland Annual Reports). Unfortunately, detailed epidemiological and obstetric data is not routinely collected on these infants. While we accept the limitations of the study group (ie data is only available on preterm births that resulted in a perinatal loss) and also its comparison group (ie detailed data are not collected on stillbirths born <24wks and there is often incomplete ascertainment of deaths up to 28 days), it was still felt to be an important exercise that might raise some interesting observations that may warrant further investigation. Acknowledging these limitations, the following section outlines the principle findings of the study.

Results

The study group included a total of 459 normally formed infants, weighing 401-1500g and/or 22-29wks gestation who died within the first 28 days of life. This group of infants was compared to 1420 normally formed infants who were either stillbirth (BW ≥500g and/or ≥24wks gestation) or who were liveborn but weighed >1500g and were >29 wks gestation.

Maternal Characteristics

With respect to the 459 infants in our study population, the mean age of the mothers at the time of delivery was 32 years (range 17-49 years) and the majority (72%) were white Irish. The age profile and ethnicity of the study group were similar to the comparison group (p-values of 0.10 and 0.34 respectively). The age profile of both the study and comparison group reflected that of the general population of mothers. However, Irish Travellers, Asian and Black Ethnicities were over-represented in the study population (11%) and in the comparison group (10%) when compared to the ethnic breakdown of the 15-49 year old national female population. A total of 17% of mothers in the study group smoked at the time of booking similar to the comparison group (17% vs 21%, p-value=0.14). The prevalence of smoking during pregnancy for Irish women is not known. The body mass index of the study group was similar to the comparison group and reflected that of women from the general population who participated in the 2015 Healthy Ireland Survey.[1] Neither underweight nor overweight/obese women were over-represented in the study group. Of note, 17% of the women in the study group reported that their pregnancy was the result of fertility treatment and this was significantly different to the comparison group (17% vs 5%, p-value<0.001). In addition, 34% of the pregnancies in the study group was a multiple gestation (twins or greater), almost 4 fold greater than in the comparison group (8%) and again this finding was highly significant (p-value <0.001). Of the 158 multiple gestations in the study group, over a quarter (28%) were as a result of fertility treatment (n=44/126, data missing for 32 cases).

In the study group, among women who had a previous pregnancy, 12% of mothers had experienced a previous preterm birth or mid-trimester loss compared to only 5% of the comparison group (p-value<0.001). In 68% of the study group, the pregnancy was complicated by spontaneous premature labour compared to 5% in the comparison group (p-value<0.001). Premature rupture of membranes was reported in 34% of the study group as opposed to 4% in the comparison group (p-value<0.001) and in almost a quarter of these cases (22%), the membranes were ruptured for >24 hours. The corresponding figure was 3% for the comparison group (p-value<0.001). Hypertensive disorders of pregnancy were reported to be less common in the study population (5% vs 8%, p-value 0.04). There was no difference between the 2 groups with regards to the incidence of pre-existing medical problems in the mother or a history of alcohol or drug abuse.

Labour onset differed markedly between the groups (p<0.001). In the study group, the vast majority of mothers had spontaneous labour (81%), only 4% had induced labour and the remaining 15% were delivered pre-labour whereas only 30% of mothers in the comparison group went into spontaneous labour, most were induced (56%) and 14% were delivered pre-labour. This difference in labour onset reflects the practice of inducing labour for most women with an antepartum stillbirth so they may deliver vaginally, as is recommended. A total of 71% of the study population and 81% of the comparison group were delivered vaginally. Not surprisingly, a significantly higher proportion of the study group delivered in a tertiary unit (67% vs 50%, p-value<0.001) and 16% of mothers were transferred antenatally to another centre as opposed to only 4% in the comparison group (p-value<0.001).

Foetal Characteristics

There were significantly more male infants born in the study group compared to the comparison group (58% versus 52%, p-value=0.04). While foetal growth restriction (<10th centile) was over-represented in the study group, it was still significantly less common than in the comparison group (26% vs 46%, p-value<0.001).

Maternal and Foetal Conditions that were present during pregnancy and reported to be associated with the death of the infant

On reviewing the maternal and/or foetal conditions that were present during the pregnancy and reported to be associated with the death of the infant, infection (either maternal infection or ascending infection) was over-represented in the study group (30% vs 9%, p-value<0.001). Despite hypertensive disorders of pregnancy being less commonly reported in the study population (5% vs 8%), it was found that these conditions were more likely to be reported to be associated with the death of an infant in the study group (2% vs 0.8%, p-value<0.001). In contrast, antepartum

or intrapartum haemorrhage (11.5% as opposed to 3.5%, p-value<0.001), specific placental conditions (30% vs 5%, p-value<0.001) and mechanical issues such as cord compression, malpresentation and uterine rupture (10% vs 1%, p-value<0.001) were all more commonly seen in the comparison group. Examination of the placenta, which was performed in 95% of cases, documented histological evidence of chorioamnionitis in 37.5% of the study group as opposed to only 11% of the comparison group (p-value<0.001).

Discussion

Preterm birth (PTB) (<37wks gestation) is one of the leading causes of perinatal morbidity and mortality worldwide. Preterm births are said to account for 75% of perinatal mortality (with about 40% of these deaths occurring in those delivered <32wks gestation) and more than half the long-term morbidity.[2, 3] Each year, in Ireland, approximately 6.5% of infants are born prematurely (5% for singleton births and 55% for multiple births) and, in 2016, they accounted for 69% of all perinatal deaths in Ireland (with 41% of these deaths occurring in those delivered <32wks).[4, 5] The obstetric precursors leading to preterm birth include: (1) delivery for maternal or foetal indications, in which labour is either induced or the infant is delivered by pre-labour Caesarean section; (2) spontaneous preterm labour with intact membranes; and (3) preterm premature rupture of membranes irrespective of whether delivery is vaginal or by caesarean section. It is estimated that about 30-35% of preterm birth are induced, 40-45% follow spontaneous preterm labour and 25-30% follow PPROM.3 National data on the reasons for PTB in Ireland are not available. In 2017, the National Maternity Hospital, in their annual neonatal report, noted that amongst their VLBW population, preterm labour accounted for 17% of PTBs, PPROM for 19% and the remaining 64% of cases were due to maternal or foetal reasons.[6] The fact that "indicated" PTB was so high in this centre may reflect its role as a tertiary referral centre for complex obstetric care. In our study group, 81% of women were reported to have gone into spontaneous labour and only 15% were delivered before the onset of labour. Clearly, there is a need for better national data as to the reasons why Irish women deliver prematurely.

This audit has raised some very interesting findings on PTB and its contribution to perinatal mortality rates in the Irish setting. If we were able to impact on the rate of preterm delivery (either spontaneous preterm delivery or medially indicated preterm delivery), the corrected PMR in Ireland could be reduced by almost 20% and the impact would likely be even greater if late neonatal deaths were included. Whilst an exhaustive review of the causes of preterm birth and its management is beyond the scope of this commentary, I wish to make a number of observations, not necessarily in order of their importance, which I believe should be highlighted at a national level. It is interesting to note that many of these observations/recommendations have already been raised in previous commentaries which have focused specifically on stillbirths. It is clear that there is a lot of common ground between the two issues. PTB (like stillbirth) is a major issue. It affects a significant number of babies and their families. Families need to be aware of the risks. Equally, healthcare professionals and Public Health services have a duty to inform and educate the public (and all future parents) about these risks and to prioritise maternity services, audit and research into this critically important area if improvements in outcomes are to occur.

1. Perinatal Audit

All 19 centres delivering infants in this county now contribute anonymised data to the NPEC on all VLBW infants in Ireland (using the Vermont Oxford Network (VON) database collection tool) and these infants are the subject of an annual report. The NICORE (Neonatal Intensive Care Outcomes Research and Evaluation) group, a group of consultant neonatologists and paediatricians with formal representation from all 19 tertiary, regional and peripheral neonatal centres in the Republic, oversee this audit and are very keen to link the data with 2 year neurodevelopmental follow up. It can only be through the rigorous collection of data including detailed follow up that we can identify areas from improvement in neonatal care. One criticism of the VON database collection tool is that it collects minimal obstetric information and so it is not possible to elucidate why a particular infant delivered preterm. Based on a recently published report incorporating three years of VON data, some interesting differences were noted between the Irish and VON population.[7] A higher proportion of multiple gestation (35% vs 27%, p-value<0.001), chorioamnionitis (16% vs 13%, p-value<0.001) and major congenital

anomaly (8% vs 5%, p-value<0.001) was found among VLBW infants born in Ireland but maternal hypertension was less commonly seen (27% vs 30%, p-value<0.001). These observations warrants further research and investigation. These findings are also supported by information derived from our study group where 34% of pregnancies was a multiple gestation and maternal infection (which includes chorioamnionitis) was reported as an associated factor with the pregnancy and/or death of the infant in 30%. Why are more multiple gestations seen in the Irish population? Is it due to assisted reproductive technology (ART)? Is chorioamnionitis more prevalent in our population and why? By seeking answers to these questions, we may be able to offer improved management and care. As we are a small country that has already a well-established national collection system for perinatal deaths and VLBW infants, we should now consider expanding the VON database to incorporate vital pieces of obstetric information. This would greatly enhance the quality and usefulness of our annual reports.

2. Primary Prevention of Preterm Birth and the role of Public Health Education

The identification of women at risk of preterm birth is important. Unfortunately, spontaneous PTB (sPTB) is a heterogeneous condition with multiple underlying aetiologies. However, it is worth drawing attention to some baseline patient characteristics, some of which were observed on our study population that may be amenable to primary intervention and result in a reduced risk of delivering a baby preterm.

Smoking has been significantly associated with preterm delivery with a meta-analysis of 20 prospective studies finding a relative risk (RR) of 1.27 with a 95% Confidence interval (CI) of 1.21-1.33 among women who smoked during pregnancy compared with non-smokers.[8] In our study, 17% of women reported smoking at booking but comparative figures for the pregnant population are not available. It would seem prudent to support all pregnant women to quit smoking especially those at high risk of delivering a preterm infant.

The relationship between alcohol and illicit drug use during pregnancy and preterm birth is less clear. While no differences were noted between our study group and the comparison group, in light of the adverse foetal effects of alcohol use, it is not unreasonable to counsel women to consider abstaining entirely from alcohol during the periconception period. Cocaine and opiod abuse has also been associated with preterm birth with relative risks ranging from 2.8-3.5 compared to non-abusers. Women in maintenance methadone programmes are also at risk of preterm birth with a RR of 2.47 compared with patients not on opiates.[9]

Pre-pregnancy maternal medical co-morbidities such as diabetes, hypertension and lupus can increase the risk of adverse pregnancy outcomes including indicated preterm birth.[10, 11] The impact of improved control of underlying maternal co-morbidities prior to pregnancy on the rate of preterm delivery is uncertain.[12] However, as pre-pregnancy control of chronic medical disorders is related to overall maternal health and may be related to other adverse pregnancy outcomes, optimising control of diabetes, hypertension and other co-morbidities is to be encouraged prior to pregnancy.[9] Once again, our study group was not found to differ from the comparison in terms of the presence of pre-existing maternal conditions.

Both maternal pre-pregnancy overweight and underweight can impact on a woman's risk of preterm birth.[13] Low pre-pregnancy body mass index (<19.5kg/m2) was associated with an increased risk of both spontaneous and indicated preterm birth compared to women of normal weight in a meta-analysis of 78 studies.[14] Pre-pregnancy overweight was associated with higher rates of indicated preterm birth but not spontaneous preterm birth.[15] Neither of these risk factors was identified in our study group.

Birth spacing has an impact on the outcome of subsequent pregnancies. The association between interpregnancy interval, (typically defined as the amount of time between delivery of the first pregnancy to conception of the second pregnancy) and preterm birth forms a J-shaped curve with the highest risk of adverse outcomes in pregnancies following very short or very long intervals.[16] The optimal interpregnancy interval associated with the lowest risk of preterm birth appears to be 18-23 months. A meta-analysis of 67 studies found that pregnancies conceived after a very short (<6 months) interpregnancy interval are at highest risk of preterm birth compared with pregnancies with an interpregnancy interval of 18-23 months.[16]

This information is not routinely collected in our annual audit.

Multiple gestations carry a substantial risk of preterm delivery and account for around 15-20% of all preterm births. In Ireland, in 2016, twin or higher order multiple births accounted for approximately 4% of all births reported and 55% of these infants delivered prematurely.[4] Multiple births accounted for 9% of all perinatal deaths in Ireland in 2016.[5] About 40% of twins will have spontaneous labour or PPROM before 37wks gestation with others having an indicated preterm delivery because of pre-eclampsia (PET) or other maternal and/or foetal disorders.[3] Nearly all higher multiple gestations will result in preterm delivery. Uterine over-distension, resulting in contractions and PPROM is believed to the causative mechanism for the increased rate of sPTB.[17] There was a very high rate of multiple gestations in our study population and the reasons for this need to be examined further.

Assisted Reproductive Technology (ART) can also impact on the rate of preterm birth. Research has shown that singletons conceived by In Vitro Fertilisation (IVF) have an increased risk of PTB compared to those conceived spontaneously.[18] As the number of women achieving pregnancy through IVF or intracytoplasmic sperm injection (ICSI) is increasing worldwide, it is important to understand the causes of PTB in these patients. A recent meta-analysis of cohort studies of singleton pregnancies conceived after IVF/ICSI reported an increased risk, of about 80%, of sPTB at both <37wks and <34wks gestation in pregnancies conceived by IVF/ICSI compared with those conceived spontaneously.[19] This is separate from the increased risk of indicated PTB in this population which is also reported. Common indications for indicated PTB in IVF/ICSI singleton pregnancies include hypertensive disorders, foetal growth restriction, antepartum haemorrhage, congenital anomalies and/or maternal request/anxiety.[20] The characteristics of the infertile population (infertility or, more likely, its causes) or the types of infertility treatment received could contribute to the increased risk of PTB. The incidence of PTB in a cohort of singleton IVF pregnancies appeared to be identical to that of matched controls achieving pregnancy spontaneously while waiting for IVF treatment and higher than that in the general population suggesting that infertility in itself is a risk factor for PTB.[21] However, a more recent study found that sub-fertile patients and non-IVF ART patients had a risk of PTB quite similar to that of fertile women, whereas the odds ratio of PTB for IVF/ISCI pregnancies was 1.55, suggesting that the risk of PTB in IVF/ISCI patients is due to the treatment itself.[22] Another reason for the higher rate of PTB in this population is due to the increased risk of multiple gestations associated with the treatment. Because if this, it is strongly advocated that single embryo transfers be performed as these give a lower rate of preterm birth compared to double or multiple embryo transfers.[23] Again, this is an area that warrants further investigation in the Irish setting.

3. Risk Assessment and Provision of Individualised Care Plans for Women at increased risk of PTB

In this section, we will focus of 2 groups of women who are at increased risk of PTB to see if there are ways to reduce that risk. The first group of women are those who have previously delivered a preterm baby and the second group of women are those who present with symptoms of threatened preterm labour. While the significant majority of the latter group of women do not go on to deliver prematurely, the clinical dilemma is to try and identify those who will at the time of their initial presentation.

With regards to the first group, it is widely accepted that one of the primary risks for preterm birth is the prior delivery of a preterm baby and this finding was born out in our study group where 12% of the women has suffer a previous preterm birth or mid-trimester loss as opposed to 5% in the comparison group. In a study by Iams at al, the risk of recurrent preterm birth <35wks varied between 14-15% as opposed to women with a previous history of an uncomplicated term delivery who had a 3% risk of spontaneous preterm delivery.[24] A recent meta-analysis reported an absolute risk of recurrent spontaneous preterm labour at <37wks gestation of 30%. Additionally, the absolute risk of recurrence appears to be substantially higher if the underlying aetiology was PTL as opposed to PPROM (a recurrence risk of 7% was reported if due to PPROM as opposed to a recurrence risk of 23% if due to sPTL).[25] Recently, in Ireland, we are seeing the emergence of specialist preterm labour clinics. These clinics assess women who have experienced a previous preterm delivery, have a known uterine malformation or have

had two or more cervical surgical procedures. In many cases, these women are seen in clinic at 10-12wks gestation or ideally even prior to conception. While frequent provider contact alone has not been shown to impact on recurrent preterm birth, social support and interventions targeted at specific risk factors have been found to have the potential to decrease the risk for recurrent preterm birth.[26, 27] Again, while not an exhaustive list of all that can be offered to an individual woman attending such a clinic, the following outlines some of the possible interventions available which can allow clinicians create an individualised care plan according to the specific circumstances.

Firstly, intrauterine infection is known to play a role in spontaneous preterm birth.[3] Micro-organisms can access the intrauterine space by ascending through the cervix from the vagina spreading intra-abdominally through the fallopian tubes or haematogenous spread across the placenta. Local and systemic infections such as bacteriuria, bacterial vaginosis (BV) and periodontal disease have been identified as risk factors for preterm birth.[3, 28] Lower genital tract infections with gonorrhoea and chlamydia have also been associated with a two to three fold increased risk of preterm birth suggesting that women with risk factors for sexually transmitted infection should be screened during pregnancy to allow early treatment and decrease the risk of preterm birth.[29] Another potential source of ascending intrauterine infection is BV. The shift in vaginal flora from predominantly lactoabacilli to predominantly anaerobic organisms has been associated with a 1.5-3-fold increased risk of preterm birth.[3] However, a Cochrane review of 21 randomised controlled trials found that antibiotic treatment of BV did not impact the rate of preterm birth in treated versus untreated women.[30] In a recent study from 2015, 248 out of 4283 low risk women were screened positive for asymptomatic bacteruria of whom 40 were randomly assigned to treatment with nitrofurantoin and 45 to placebo. No difference in the rate of PTB was noted.[31] Because of the conflicting literature, most of these high risk clinics do screen women for genital infection and often consider a course of treatment if specific organisms are found. It is notable that infection was reported to be an associated factor in 30% of our study group and this is clearly an area that warrants further research.

Multiple randomised controlled trials have suggested a beneficial effect of 17αhydroxyprogesterone caproate (17OHPC) for prevention of recurrent preterm birth.[32] While the mechanism of action is uncertain, possibilities include modulation of inflammation, maintenance of cervical integrity and relation of uterine smooth muscle.[12] A randomised controlled trial of 463 women with prior preterm birth given weekly infections of 250 micrograms of 17OHPC versus placebo from 15-36wks of gestation found a significant reduction in delivery prior to 37wks (36.3% vs 54.9%).[33] A recent study, the OPPTIMUM study looked at the role of vaginal progesterone prophylaxis for preterm birth. This was the largest retrospective, double-blinded study of its kind. Although no harmful effects were noted, there was no significant value attributed to vaginal progesterone, particularly in women with a short cervix. The study did suggest that there was a "general trend" towards benefit and perhaps even significance may have been shown if such a large proportion of patients had not been lost to follow up.[34] A Cochrane Review in 2013 including 11 studies encompassing 1899 singletons with a prior spontaneous preterm birth reported a significant reduction in spontaneous preterm birth <34wks (RR 0.31: 95% CI: 0.14-0.69) in those women treated with progesterone (by any route).[35] Currently, the recommendation is that women with a prior spontaneous preterm birth should receive vaginal progesterone daily or 17OHPC intramuscularly weekly starting from around 16wks gestation.

Of women with a history of a prior sPTB, those with a short cervix appear to be at the highest risk.[36, 37] Furthermore, a prospective blinded observation study was conducted in which women with a previous sPTB <32wks gestation and a current singleton pregnancy underwent serial cervical length (CL) assessments.[38] The investigators found that CL <25mm as a single measurement at 16-18 wks gestation was associated with a RR of sPTB of 3.3 (95% CI: 2.1-5.0) and the inclusion of serial observations of CL until 23wks 6 days significantly improved the predictions compared to an isolated measurement. Consequently, serial CL screening for women with a singleton pregnancy and a history of sPTB is generally recommended. In a multicentred trial of 302 women with prior preterm birth <34wks gestation and a CL <25mm randomised to cerclage or no cerclage, the risk of perinatal morbidity was significantly reduced with cerclage and preterm delivery <35wks gestation was significantly reduced with cerclage in the subgroup of women with CL <15 mm.[39] The benefit of cerclage in women with a shortened

cervix and prior preterm birth was subsequently supported by a meta-analysis of five trials.[40] While history-indicated cerclage (cerclage placed at 12-14wks based on prior history alone) has been advocated for women with prior early preterm or periviable delivery, serial screening cervical lengths with placement of cerclage only if a shortened cervix is detected is equally efficacious and results in 60% fewer cerclage placements based on a meta-analysis of four trials.[41] Based on the existing literature, it would seem prudent to perform serial assessments of CL from 16-24wks gestation in women with a history of sPTB <34wks gestation with a plan for an ultrasound-indicated cerclage if a short cervix (<25mm) is identified.

Women who present with a history of indicated preterm birth due to pre-eclampsia or foetal growth restriction have an elevated risk of recurrent indicated preterm birth.[42] Daily dose aspirin started prior to 16wks of gestation has been studied to decrease the risk of recurrent pre-eclampsia or placental insufficiency. It is, therefore, not unreasonable to commence daily aspirin from 12wks of pregnancy in women with one or more high-risk condition such as prior pre-eclampsia, hypertension, diabetes, renal disease or lupus.[43]

The second group of women to consider are those presenting with symptoms suggestive of preterm labour (PTL). If it were possible to predict imminent birth among these women before advanced cervical dilatation, then it would be possible to administer antenatal steroids and to arrange an antental transfer to a tertiary neonatal centre if required.

Fetal fibronectin (FFN) is an extracellular matrix glycoprotein found in the amniotic membrane, decidua and cytotrophoblasts. It can be detected in cervical and vaginal secretions in all pregnancies, but elevated levels (≥50ng/ml at >22wks gestation) has been associated with an increased risk of sPTB.[44] The efficacy of FFN in the prediction of sPTB has been assessed in several populations but here we will primarily focus on those studies that included women with suspected PTL. Initially, it was hoped that the use of qualitative FFN testing alone in symptomatic women with singleton gestations would allow accurate identification of women with true preterm labour versus those with false labour. In the largest multicentre observational study of women with symptoms suggestive of PTL, compared to women who had negative FFN results, those who had positive FFN results were more likely to deliver within 7 days (RR 25.9, 95% CI: 7.8-86), within 14 days (RR 20.4, 95% CI: 8.9-53) and before 37wks gestation (RR 2.9, 95% CI: 2.2-3.7).[45] However, the predictive value of a positive FFN results was only 13% for delivery within 7 days of presentation. The most promising finding was that the negative predictive value for delivery within 7 days was very high at >99%. Despite observational studies that suggested FFN testing may help reduce the use of unnecessary resources, RCTs have not confirmed these findings. In a systematic review and cost-analysis of five RCTs, and 15 diagnostic test accuracy studies, FFN testing was found to have moderate accuracy for predicting PTB but no RCT reported a significant improvement in maternal or neonatal outcomes.[46] In their base-case cost analysis, there was a modest cost difference in favour of FFN testing but this was largely dependent on whether or not FFN testing reduced hospital admissions which varied significantly. A 2016 systematic review and meta-analysis of six RCTS that included 546 women with singleton gestations who presented with PTL symptoms found that those randomly assigned to knowledge of FFN results did not have reduced rates of PTB at <37wks, <34wks, <32wks or <28wks when compared to the control group.[47] Equally, women who were randomly assigned to knowledge of FFN results had similar rates of hospitalisations, use of tocolytics and receipt of antenatal corticosteroids when compared to the control group (no knowledge of FFN results). Contrary to prior studies, mean hospital costs were actually slightly higher in the group randomly assigned to knowledge of FFN. It would seem that based on the current evidence, there is no reason to justify the routine use of FFN alone in women with threatened PTL.[48]

More recent studies have focused on quantitative measurement of FFN hoping that this may improve the predictive values when compared to the qualitative tests that use 50mg/ml as the threshold.[49, 50, 51] In a pre-specified secondary analysis of a prospective blinded study, the PPV for sPTB <34wks gestation increased from 19%, 32%, 61%, 75% with increasing thresholds (10, 50, 200 and 500 ng/ml respectively).[49] At the moment, the use of quantitative FFN remains investigational.

Placental alpha microglobulin-1 (PAMG-1) is another biomarker (like FFN) which is assessed by a bedside test, PartoSure, making it very

user friendly in a clinical situation. This had been compared to FFN and cervical length measurement and it has been reported that PAMG-1 was more accurate in predicting PTB within 7 days with 80% sensitivity and 95% specificity with the greatest utility in patients whose cervical length was 15-35mm.[52] A recent meta-analysis comparing PAMG-1, FFN and phosphorylated Insulin-like Growth Factor Binding Protein-1 (phIGFBP-1) in symptomatic women reported that PAMG-1 had the highest PPV and positive likelihood ratio while the negative predictive value and negative likelihood ratio remained similarly high between the three biomarkers.[53]

It would seem that the real value of these biomarkers in the Irish context is not so much in their ability to predict imminent delivery but more in their ability to determine which women are most likely not to deliver (Ie their high negative predictive values). In the context of a negative test, it is unlikely that a women with deliver within 7 days. This means that unnecessary treatments and admission to hospital can be avoided. One of the difficulties faced by many neonatologists working in tertiary centres in Ireland is the inability to accept in utero transfers of high risk pregnancies from around the country because of a lack of antenatal beds. The use of the aforementioned biomarkers would assist clinicians in determining which mothers are best transferred to tertiary centres ensuring better utilisation of a limited resource even if it is accepted that many of the women transferred will not deliver within 7 days. Data from the 3 year report on mortality of VLBW infants born in Ireland noted a reduced mortality for infants <28wks gestation who delivered in a tertiary neonatal centre.[7] This report's recommendation, which was in line with the existing Model of Care for Neonatal Services in Ireland, was that infants <28wks gestation should ideally be delivered in a tertiary neonatal centre.[7] It is my opinion that we should advocate for the use of one of these tests in the setting of threatened PTL to better determine which mother should be transferred.

The role of cervical length (CL) measurement in the assessment of women who present with PTL symptoms has also been studied. A 2016 systematic review and meta-analysis of RCTs using individual patient-level data concluded that knowledge of CL in women with symptoms of acute PTL was associated with a significant reduction in PTB <37wks (RR 0.64, 95% CI: 0.44-0.94).[54] However, other outcomes, including PTB at early gestations, time from randomisation to delivery, time from evaluation to discharge and other neonatal outcomes were not statistically different between those in whom there was knowledge of CL as opposed to those who were managed without that information. Therefore, the role of CL measurement in this population remains unclear. As a country that is already stretched and unable to provide routine ultrasonography to all woman in the second trimester of pregnancy, it is doubtful that Irish maternity services are currently in a position to incorporate the routine assessment of CL in this population until there is more compelling evidence for its use.

4. Detection of Foetal Growth Restriction (FGR)

As a neonatalogist, I would strongly support the NPEC and my obstetric colleagues in their many calls to improve detection of foetal growth restriction (FGR) and small for gestational age (SGA) in pregnant Irish women. The Institute of Obstetrics and Gynaecology in collaboration with the Royal College of Physicians of Ireland and the Directorate of Strategy and Clinical Programmes of the Health Service Executive published Clinical Practice Guideline No. 29 in 2014 on Foetal Growth Restriction – Recognition, Diagnosis and Management. Without doubt, improved antenatal detection of FGR with timely delivery is a preventative strategy to reduce perinatal mortality. The NPEC has called on many occasions for the generation of customised birth weight centile charts for every woman during pregnancy in addition to staff training in risk assessment, plotting of symphysial fundal height and scan weight estimates. While this may result in more infants being born preterm, these infants tend to be born in better condition with less significant morbidities and this should hopefully improve their chances of survival without associated disability.

5. Investigations to determine the cause of preterm birth

Again, as is currently done with every case of a perinatal loss, I would advocate a similar systematic approach to every women who delivers a preterm infant in Ireland especially those who deliver <32-34wks gestation. This should include, but not necessarily be limited to, a review of maternal risk factors amenable to intervention, a review of the obstetric details leading to the preterm delivery in addition to a thorough examination of the placenta. Review of placental pathology from the index preterm case may further elucidate a woman's risk of recurrent preterm birth. Placentas from spontaneous preterm births are more likely than those from indicated preterm births to exhibit acute inflammation of the membranes, chorionic plate and umbilical cord.[55, 56] The presence of inflammatory lesions on placental pathology is associated with an increased risk of recurrent preterm birth (RR 2.4, 95% CI: 1.2-4.7) compared with women without inflammatory lesions.[55] Placental examination may also support a diagnosis of placental insufficiency and so may lead clinicians to recommend aspirin in a subsequent pregnancy.

In summary

1. PTB is a significant contributor to perinatal mortality and morbidity in Ireland
2. The two current audits (Perinatal Mortality and VLBW Infants) should be expanded to include a more detailed maternal risk factor assessment and more detailed obstetric information. The NPEC should also extend its collection of data to all pregnancies delivering ≥22wks gestation irrespective of the outcome of the pregnancy (ie liveborn or stillbirth).
3. Consideration should be given to the establishment of a national working group to include Obstetricians, Neonatalogists, Midwives and Allied Health Professionals whose remit is to look at the problem of PTB in Ireland at a national level and how it is best addressed.
4. The establishment of high risk specialist clinics for women at risk of recurrent PTB is to be strongly encouraged.
5. Maternity Units should strongly consider the use of a biomarker to better determine which mother, who presents with threatened preterm labour, should be transferred to a tertiary centre.
6. More resources, including in the area of antenatal ultrasound, are urgently required.
7. Placental Examination should form part of the work up in the case of any woman who delivers a baby <34wks gestation.
8. As with every perinatal death, consideration should also be given to establishing a confidential enquiry into any infant <28wks who delivers outside a tertiary neonatal centre. This would lead to a better understanding of the myriad of factors at play but could better inform the organisation of maternity services into the future.

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