Exploring modifiable risk-factors for premature birth in the context of COVID-19 mitigation measures; A discussion paper

Abstract

During the COVID-19 pandemic, parents with sick or premature babies have faced challenges following admission to a neonatal unit due to the imposed lock-down restrictions on social contact, hospital visitation and the wearing of personal protective equipment. The negative short-term impact on neonatal care in relation to the prevention of proximity, contact and bonding between parents and babies is potentially significant. However, an interesting finding has been reported of a reduction in premature birth admissions to the neonatal intensive care unit during the pandemic, raising important questions. Why was this? Was it related to the effect of the modifiable risk-factors for premature birth? This discussion paper focuses on an exploration of these factors in the light of the potential impact of COVID-19 restrictions on neonatal care. After contextualising both the effect of premature birth and the pandemic on neonatal and parental short-term outcomes, the discussion turns to the modifiable risk-factors for premature birth and makes recommendations relevant to the education, advice and care given to expectant mothers.

Introduction

COVID-19 has changed the world. It has changed how people work, do business, provide and receive education, socialise and communicate. It has separated families and friends. It has changed how pregnant women and their partners receive support during pregnancy, labour, birth and in the postnatal period. Within the neonatal setting, parents with sick or premature babies have faced challenges following admission to a neonatal unit following restrictions to social contact, hospital visitation and the wearing of personal protective equipment (PPE)

(Royal College of Paediatrics and Child Health (RCPCH), 2020) (Table 1). While the longer-term impact of such lock-down restrictions on neonatal care are yet to be fully known, there are negative immediate and short-term effects, in relation to the prevention of proximity, contact and bonding between parents and their babies (Green et al, 2020a; Stuebe, 2020). However, it has been reported in three simultaneous, independent European studies (Been et al, 2020; Hedermann et al, 2020a, b; Philip et al, 2020) that admissions of premature babies to the neonatal intensive care unit (NICU) have reduced during the pandemic raising certain questions. Firstly, was this merely a coincidence? Secondly, were there fewer babies born prematurely who needed intensive care?

It is certainly too early in the pandemic to answer the latter question and indeed, to know if this pattern will continue. Other studies have also concluded differently, their findings showing *higher* rates of premature birth in COVID-19 positive women (Allotey et al., 2020; Antoun et al., 2020; Dubey et al., 2020; KC et al. 2020). However, the research by Been et al (2020), Hedermann et al (2020) and Philip et al (2020) has focused on the impact of mitigation measures rather than infection as a causative agent for premature birth. Moreover, the findings have raised an area for consideration and further discussion in addressing another question; if fewer premature babies were being born during lock-down, why was this? As these authors and related commentary suggest (Cullen, 2020; Kearney and Kendall, 2020) a possible effect of certain restrictions on the modifiable risk factors for premature birth, this offers us an ideal opportunity to explore these further, learn from them and make tailored recommendations relevant to the education, advice and care given to pregnant mothers.

Table 1: COVID-19 Mitigation measures
▪ Social distancing ▪ Advice against social interaction and visiting ▪ Advice against handshaking/physical touch ▪ Regular handwashing/use of alcohol hand-gel ▪ Advice for staying at home when experiencing symptoms or when having been in contact with COVID-19-positive person or having visited a high-risk area ▪ People need to stay home if symptomatic (fever, respiratory complaints) ▪ Closing of schools and childcare facilities ▪ Reduced commuting to and from work/homeworking ▪ Personal protective equipment (PPE) - particularly wearing of face masks

The impact of premature birth

It is estimated that 1 in 10 babies are born preterm worldwide (WHO, 2017). It is significant that prematurity is the leading cause of death in newborns under four weeks of age, and preterm birth complications are the leading cause of death among children under five years of age (WHO, 2018). Added to the complexity, many of these babies may have impaired short and long-term outcomes relating to cognitive, social–emotional, mental health, behavioural, and regulatory difficulties into school age and beyond (Altimier et al., 2016).

Premature birth can also be a major life stressor for parents. Following the birth, the parents find themselves in an unfamiliar and technological environment which can be overwhelming, as they adjust to their new role as parents of a premature baby. Parents can grieve the loss of their expected pregnancy length, and the early arrival of a baby whose survival and immediate and long-term future outcome is uncertain (Aagaard et al., 2015; Fowler et al., 2019). The baby's appearance can be a source of distress and could impact on their ability to bond with the baby (Green et al., 2015). Parental bonding is facilitated with behaviours such as a bedside vigil, touching, holding and interventions such as kangaroo care (Aydon et al., 2017).

It is often not until the baby is taken home that the parents become aware of the unique needs of the growing premature baby and the higher level of care required. Due to their initial prematurity, coupled with an immature immune system, they are at significant risk for hospital readmission (Roberts and Cheong, 2014). The transition home of extremely premature babies can be fraught with difficulties as outlined by Green et al. (2020b). Maternal mental health is fundamental to the well-being and development of the premature baby, both in the NICU and at home, however mothers of premature babies have been found to have higher rates of depression, anxiety, acute and post-traumatic stress reactions (Baum et al., 2012). Evidence is also mounting that babies less than 1000 grams are at an increased risk of mental health problems in childhood, adolescence and adulthood (Johnson and Marlow, 2014; Altimier et al., 2016). Health professionals have been shown by Petty et al. (2018; 2019) to not always have an optimum understanding of the needs of growing premature babies, which further increases maternal anxiety; in fact, Fowler et al. (2019) referred to parents as *"the forgotten mothers of extremely premature babies"*.

Within the above context, it would be a great achievement, and have significant public health benefits, if the number of premature births could be decreased (Frey and Kiebanoff, 2016) reducing the risk of lengthy NICU admissions and the risk of poor neurodevelopmental outcomes and disabilities. It could also lower the number of re-admissions to hospital and have a positive impact on parenting ability. No doubt the financial impact on the family and society would also be beneficial as less resources would be required in the short and long-term.

The impact of COVID-19 on neonatal care

During the COVID-19 pandemic, there has been a substantive impact on the interactions between infants, parents, health professionals and nurses. For example, at what is already a stressful time, the use of PPE has meant that the interpretation of non-verbal cues, particularly facial expressions has been reduced, thus limiting some important aspects of communication. Social distancing has meant that staff have been unable to physically comfort parents and their infants as they would normally. In addition, family support that is frequently key to the parent-infant bonding process, has been reduced as a result of restricted visiting to the neonatal unit. These factors provide a range of additional challenges to all concerned, especially parents whose anxiety levels may be further heightened.

However, an interesting and a more positive outcome of the COVID-19 virus has been reported from Ireland (Philip et al., 2020), Denmark (Hedermann et al., 2020a, b) and the Netherlands (Been et al., 2020) of an unprecedented fall in preterm births. The University Hospital, Limerick has reported a 73% reduction in the number of very low birth-weight babies born in the hospital, when compared to the same period in the previous two decades (Philip et al, 2020). The Danish study found the birth rate of extremely premature infants decreased significantly during the nationwide lock down, again compared to the preceding five years (Hedermann et al., 2020). Been et al (2020) most recently found that numbers of preterm births greatly reduced in the Netherlands following implementation of mitigation measures against the effects of the COVID-19 pandemic. They studied the impact of these measures in a stepwise fashion on the incidence of preterm birth using data from the neonatal dried blood spot screening for 56, 720 births that occurred after implementation of COVID-19 mitigation measures on March 9, 2020. Consistent reductions in the incidence of preterm

birth were seen across various time windows surrounding March and no changes were observed after March 23.

The reduction has been credited to the possible effect of positive lifestyle influences during isolation and COVID-19 restrictions with reduced exposure to ordinary stressors at work, less commuting, increased family support, better infection avoidance, improved sleep, nutrition and exercise, and lower exposure to tobacco and illegal drugs (Cullen, 2020). The Denmark research identified similar factors, suggesting the risk factors for premature birth, such as increased systemic maternal inflammation and other immunologically mediated processes, may be negated by the increased focus on hygiene, physical distancing, and home confinement during the lockdown (Hedermann et al., 2020a).

Been et al (2020) would agree and state that many of the known risk factors for premature birth may be possibly affected by COVID-19 mitigation measures. These include asymptomatic maternal infection, which through vertical transmission can cause intrauterine infection, resulting in early birth. Referring to Table 1, social distancing, self-isolation, lack of commuting, closing of schools and childcare facilities, and increased awareness of hygiene (e.g. hand washing) all reduce contact with pathogens and, accordingly, risk of infection. Been et al (2020) propose that the timing of the observed preterm birth reductions in their study suggests that hygiene measures and anticipatory behavioural changes may have contributed to the findings. In addition, closure of most businesses, homeworking may have led to less physically demanding work, less shift work, less work-related stress, optimisation of sleep duration, uptake of maternal exercise indoors and outdoors, and increased social support, which could all have a positive effect. Additionally, the decrease in air pollution caused by the lockdown restrictions may have also played a role in the observed reduction of

premature birth, as air pollution, particularly the anthropogenic PM2.5 (fine particulate matter that can remain airborne for long periods and travel hundreds of miles), is associated with 18% of premature births globally (Hedermann et al., 2020a, b).

While the decrease in the number of premature babies is good news for those who research aspects of prematurity, it is important to remember that Cullen's (2020) and Hedermann et al's (2020a, b) studies need to be interpreted with caution because these studies were not designed to demonstrate which specific factor/s was responsible for the decrease in preterm births (Kearney and George, 2020). In addition, and unfortunately, the decrease in premature births is not occurring in all countries. For example, in Nepal prior to the pandemic, premature births were 24.5% of the proportion of babies born nd this has now risen to 26.2% (KC et al. 2020). Antoun et al (2020) undertook a prospective study at an English hospital with data were analysed from 23 pregnant women who had tested positive to COVID-19. During the study, 19 women delivered with 36.8% having a premature birth. Whilst none of the infants were COVID-19 positive, the authors concluded that the virus is associated with a high incidence of prematurity, caesarean section and pre-eclampsia. However, this was a small-scale study and further research is required to fully substantiate the results. Allotey et al's (2020) and Dubey et al's (2020) systematic reviews concluded that preterm birth rates were higher in pregnant women with COVID-19 than in pregnant women without the disease.

Despite this, the abovementioned findings from Ireland, Denmark and the Netherlands, should be given thoughtful consideration, because when the COVID-19 crisis is over pregnant women will resume their lives and working patterns, not limiting social interactions and possibly standing or being active for long periods. It is unlikely that women will stay at home for the purpose of research (Kearney and George, 2020). That said, it is still of interest

to explore further the possible reasons why premature births may have been reduced in certain countries and whether we can learn more about potential measures to lesson or prevent risk factors for premature birth. The paper will now turn to a discussion of such risk factors.

Modifiable risk factors for premature birth

While it is noteworthy that many women who experience preterm birth have no risk factors identified (National Institutes for Health (NIH), 2017), a range of factors influence the *likelihood* of preterm birth (Table 2). Many risk factors are not modifiable during a woman's current pregnancy or they evolve as a complication of the pregnancy (Table 2a). However, modifiable risks (Table 2b) are those that can be controlled or altered to help reduce the risk of preterm birth, for example by making lifestyle changes. Therefore, addressing modifiable risk factors may reduce the risk of preterm birth and/or adverse pregnancy outcomes. These will now be further explored.

Infection/Inflammation

Preterm birth can be initiated by infection or inflammation. Infection and infection-driven activation of inflammatory responses are thought to be the leading risk factors of spontaneous preterm birth (Cappelletti et al., 2016). Infection has been detected in at least 25% of all cases of preterm birth, with 79% of mothers at risk of preterm birth testing positive for an infective process, leading researchers and clinicians to believe that infection-associated inflammation regulates the timing of the onset of labour (Cappelletti et al., 2016). The pathological process of inflammation has been established as a causal link with preterm birth (Tency, 2014) with increased production of pro-inflammatory cytokines associated with uterine activation and

preterm birth, and production of anti-inflammatory cytokines shown to calm the uterus during pregnancy (Cappelletti et al., 2016).

Table 2: Non-modifiable and modifiable risk factors for premature birth

2a: Non-modifiable risk factors

High-risk

- Women who have delivered preterm before
- Women who are pregnant with greater than one baby (multiple gestation)
- Women with abnormalities of the reproductive system, particularly the cervix if it is short or shortens early in the second trimester (NIH, 2017)

Lower risk

- Placenta previa where the placenta implants in the lowest part of the uterus and covers all or part of the opening to the cervix
- Rupture of the uterus is more likely with a previous caesarean delivery or removal of a uterine fibroid.
- Ethnicity with preterm labour and birth occurring more often among certain racial and ethnic groups.
- Mother's age with those younger than age 18 and those over age 35 more at risk
- Women who become pregnant through in vitro fertilization have an 80% higher risk for spontaneous preterm birth. This is unrelated to multiple gestation.
- Fetal abnormality

2b: Modifiable risk factors

- Infection/inflammation as a cause – includes urinary tract infections, dental health, sexually transmitted infections and vaginal infections, avoiding disease - Influenza vaccination
- Maternal disease processes including a pre-pregnancy type-2 diabetes, gestational diabetes and hypertension
- Life-style factors including obesity, smoking, drinking alcohol and use of illegal drugs
- Lack of antenatal care
- Work related stress with long working hours with long periods of standing
- Home related stress, lack of social support, domestic violence, including physical, sexual, or emotional abuse
- Exposure to certain environmental pollutants
- A short time period between pregnancies (less than 6 months between a birth and the beginning of the next pregnancy)

Intrauterine infection and invasion by the lower genital tract bacteria evoke an immune response that triggers prostaglandin synthesis in the amnion and chorion (Verma et al. 2014; Wynn et al. 2020). These substances trigger uterine contractions, membrane rupture and cervical ripening, leading to membrane exposure, and entry of microorganisms into the uterine cavity.

Physiological alterations in the urinary tract and immune related changes associated with normal pregnancy, predispose pregnant women to urinary tract infections (Habak and Griggs 2020). The physiologic changes in the urinary tract include dilation of the ureter and renal calyces due to the smooth muscle dilatation as a result of progesterone and ureteral compression from the gravid uterus. The ureteral dilation can be marked and, coupled with the decreased bladder capacity, urinary frequency commonly occurs. Vesicoureteral reflux may also be seen. These pregnancy related changes increase the risk of urinary tract infections (Habak and Griggs 2020); asymptomatic urinary tract infection is very common and is linked with preterm birth. Verma et al. (2014) found urogenital infection was 2.1 times (36.54 %) higher in women with preterm labour.

During pregnancy, the balance of bacteria and yeast in the vagina is altered due to the rise in oestrogen levels, and this yeast can overgrow. Bacterial vaginosis is caused by an imbalance in the normal bacteria and flora that exist in the vagina. Bacterial vaginosis has a strong positive association with preterm birth (Manns-James, 2011). Bacterial imbalance can be triggered by douching, unprotected sexual intercourse, having multiple sex partners, antibiotics and vaginal medications. Bacterial vaginosis is not transmitted as a sexually transmitted disease but is associated with vaginal intercourse. However, bacterial vaginosis increases the risk of contracting sexually transmitted infections, including the herpes simplex virus, chlamydia,

and HIV. Pregnant women with bacterial vaginosis are more likely to have a preterm birth or other adverse obstetrical outcome (Owens et al. 2020). This is problematic because the treatment of bacterial vaginosis during pregnancy has not been shown to improve preterm birth rates; it has been suggested that this is because the inflammatory cascade that directly causes increased prostaglandin production and cervical changes resulting in preterm labour may have reached a critical stage before the bacterial vaginosis is diagnosed and treated (Manns-James 2011).

Sexually transmitted infections are also associated with increased inflammation and intrauterine infection/inflammation is associated with approximately 40% of preterm deliveries (Wynn et al. 2020). Gonorrhoea and syphilis have been shown to increase the risk of early preterm birth before 32 weeks gestation. Previous work by de Attayde et al. (2011) has suggested a link between preterm birth and chlamydia, however Baer et al. (2019) did not find an association.

Periodontitis is a destructive inflammatory disease of the tissues that support the teeth caused by the oral bacterial biofilm (Saini et al. 2010). A Biofilm is a layer of bacteria that adheres to surfaces in the mouth. Periodontal disease can also worsen cardiovascular diseases and diabetes (Huck et al. 2011). Pregnancy influences periodontal status, with pregnant women being more susceptible to gingival inflammation. Women with periodontal disease prior to pregnancy have a risk of severe disease during pregnancy with hormonal changes believed to exacerbate gingival inflammation, to initiate changes in the composition of oral biofilm, and to induce a selective growth of periodontal pathogens (Huck et al. 2011). It is believed that most of the intrauterine infection originates in the lower genital tract (Huck et al. 2011). However, studies have reported intrauterine infections are caused by species not found in

urogenital tract (Huck et al., 2011). The bacterial spreading theory suggests that the bacteria that cause inflammation in the gums can enter the bloodstream and the amniotic fluid leading to chorioamnionitis and premature labour and birth (Saini et al. 2010). In periodontal disease, the inflamed tissues produce proinflammatory cytokines, mainly interleukin 1-beta (IL-1β), IL-6, prostaglandin E2, and tumour necrosis factor-alpha (TNF-α) (Saini et al. 2010). Endotoxins released from gram-negative bacteria are believed to be responsible for periodontal disease by producing cytokines and prostaglandins which stimulates labour. Proinflammatory mediators can cross the placental barrier resulting in preterm birth (Saini et al. 2010).

Pregnant women are considered vulnerable to serious influenza disease and related complications such as preterm birth and fetal death (Fell et al. 2017). Reports from the 2009 H1N1 influenza A pandemic found that pregnant women are at an increased risk for hospitalization, acute respiratory distress syndrome, and death compared to the general population. Influenza infection can trigger preterm birth, but the exact mechanism of influenza-mediated immune activation causing preterm labour has not yet been articulated (Hartel et al. 2016). Possibly more worrying for the premature baby is those who were born during influenza season had a significantly higher risk of periventricular leukomalacia, a brain injury that creates holes in the white matter (Härtel et al., 2016). The World Health Organization (WHO) has recommended influenza vaccination for all pregnant women since 2012, but the vaccination rate has been low (Bartolo et al. 2019).

Maternal disease

The role of maternal infection in preterm labour has been discussed as well as the conflicting findings on COVID-19 as either reducing or increasing premature births. But what about

other maternal disease? Diabetes, for example, can impact on the wellbeing of the mother and infant. One may argue that Type 1 diabetes is non-modifiable in that it is not related to lifestyle factors; Coton et al (2016) explain that Type 1 diabetes is frequently diagnosed in childhood and occurs as a result of the cells that produce insulin being destroyed. Women from an ethnic minority background (in particular Asian and Hispanic) are more likely to be diagnosed with gestational diabetes (Lawrence et al, 2008); those mothers who have a Black, Asian and Minority Ethnicity, again non-modifiable factors, are more prone to the effects of the COVID-19 virus so maternal diabetes could potentially further complicate their health and that of their baby.

However, Type 2 diabetes, that occurs when the body does not produce enough insulin, may be modified through dietary and bodyweight alternations. This type of diabetes has become an increasing problem with the incidence of it being more prevalent than Type 1 in pregnancy in some regions (Coton et al, 2016), hence lifestyle changes are imperative.

Unfortunately, maternal diabetes during pregnancy can mean that there are increased risks to the infant, including congenital abnormalities (Chen, 2005) and perinatal mortality (Chen et al, 2019). The incidence of prematurity in terms of Type 1 maternal diabetes has been highlighted (Lin et al, 2017). The association with Type 2 is less clear with no papers specifically identifying a link, although Hedderson et al (2003), in a cohort study of 46 230 women, concluded that gestational diabetes could slightly increase the risk of a spontaneous premature birth.

There have been different approaches to the management of maternal Type 2 and gestational diabetes during pregnancy, most specifically, the administration of insulin. Kong et al (2019),

in a Finnish study, examined data from 649 043 live births (2004–2014). Maternal diabetes, treated with insulin, was associated with an increased risk of the baby being large for gestational age and premature; however, maternal obesity in women with Type 2 diabetes only presented mild to moderately increased risks. The authors suggest that the results should be considered when considering the care and management of pregnant women with diabetes.

The impact of maternal diabetes to the infant can be substantive; Opara et al (2020) undertook retrospective research involving neonates who weighed less than 1500grms and concluded that maternal diabetes was directly linked to retinopathy of prematurity [ROP] and that that the association was greater with increased severity of ROP. On a positive note, Persson et al (2018), following their retrospective study with 76 360 infants born between 2007 and 2015, found that maternal diabetes was not associated with further increased risks for premature infants, less than 1500grms, who were being cared for in high resource settings.

Finally, in this section, it is important to briefly mention the potential impact of maternal hypertension on the infant, this may be gestational hypertension, or it may be associated with pre-eclampsia, a condition that is not yet fully understood (Cook et al, 2020; Madan et al, 2010). The aim when caring for the pre-eclamptic woman is to enable the pregnancy to proceed as far as is feasible so that the baby's prematurity is reduced (Cook et al, 2020). Chappell et al (2019) undertook research to ascertain whether an induced birth would benefit the mother without harming her baby. Women from maternity units in England and Wales, who were all pre-eclamptic, were involved in the study; 448 were in the research arm for a planned delivery and 451 were allocated to have usual care. The study reported that the early planned delivery was beneficial for the mother, did not cause harm to the infant, but that it

meant increased admissions to the neonatal unit. The findings from further are awaited as it could have implications for both maternal and neonatal care.

The health and wellbeing of the pregnant mother can have a substantive impact on the health and wellbeing of the infant. The appropriate management of the underlying maternal condition requires careful consideration and discussion.

Life-style factors

Evidence is still mounting about COVID-19 and pregnant women, however the pre-existing comorbidities, high maternal age, and high body mass index seem to be risk factors for severe COVID-19 (Allotey et al., 2020). These are also the co-morbidities or risk factors for preterm birth (NIH, 2017).

The community of microorganisms that lives on and in humans is the microbiome. The microbiota in the microbiome are both helpful and potentially harmful. Most microbiota are symbiotic with the body and microbiota benefitting, while a smaller amount are pathogenic. If the person is healthy the pathogenic and symbiotic microbiota coexist without problems (Quigley 2010; Roberfroid 2000). *Prebiotics* are a type of fibre that cannot be digested, and they serve as food for probiotics (Quigley 2010). Prebiotics are in foods such as whole grains, wheat bran, bananas, green vegetables, onions, garlic, soybeans, artichokes, leeks, barley, oats, apples flax seeds and seaweed (Roberfroid 2000). Probiotic foods contain beneficial live microbiota and include fermented foods like kefir, yoghurt with live active cultures, pickled vegetables, tempeh, kombucha tea, kimchi, miso, and sauerkraut. Labelled beneficial bacteria, probiotics may contain a variety of microorganisms, with the most common being *Lactobacillus* and *Bifidobacterium* (Roberfroid, 2000). There have been

proposals to supplement pregnancy women with probiotics to minimise the effect on the microbiome and decrease the risk of preterm birth. A review by Othman et al. (2007) found that further research was required before recommendations about preterm labour and birth could be made. It is noteworthy that probiotics given vaginally to the pregnant women reduced the number of harmful bacteria (Othman et al., 2007). It has been hypothesised that probiotics administered vaginally can displace and kill harmful bacteria by the development of inflammatory cytokines, reducing vaginal pH which encourages the growth of healthy bacteria (Buggio et al., 2019). Further benefits of the modification of gut microbiota have been reported by Nordqvist et al. (2018) as an improvement in insulin sensitivity in pregnant women. Late gestation consumption of probiotic milk was associated with a decreased risk of pre-eclampsia and a reduction in the risk of preterm birth (Nordqvist et al., 2018)

Maternal smoking is directly linked to hypertension because of the disruption of neoangiogenesis and of endothelial function within vessels (Janisse et al., 2014; Mei-Dan et al., 2015). Maternal smoking during pregnancy has been consistently reported as a modifiable risk factor for adverse perinatal outcomes including preterm birth. The preterm delivery rate was significantly higher in the smoking group compared with controls (22.2% vs. 12.4%, $P<0.05$), and even low levels of exposure of up-to-five cigarettes per day was significantly associated with preterm birth (Mei-Dan et al., 2015). Maternal smoking and preterm delivery are related because of the vasoconstrictor action of nicotine that causes a reduced blood flow to the placenta, the binding of carbon monoxide to haemoglobin making less oxygen available for placental and fetal tissues.

Maternal nutritional status may influence gestational length, and an adequate supply of maternal nutrients is necessary for continuation of pregnancy, and preterm birth can occur

when there is an imbalance between maternal and fetal needs. The rise in obesity levels within women of reproductive age has been substantive (Ng et al., 2014) and is particularly important to consider given that COVID-19 has more severe consequences for those in that category. Obesity in pregnancy is known to have a potential impact on both the mother and the baby with risk factors for the infant including prematurity and congenital abnormalities (Stothard et al., 2009; Aune et al., 2014; Catalano and Shankar, 2017; Cnattingius et al., 2013; Hadley et al., 2019). In addition, and importantly, the infants of obese mothers are more likely to become obese themselves, potentially leading to a range of health problems throughout their life course. Despite this, an absolute and direct link to maternal obesity and infant health is difficult to establish because of other variables such as lifestyle and genetic factors. The research that has been conducted is inconclusive – for example, Aly et al (2010), in their retrospective study, analysed data from mothers who gave birth at the George Washington University between 1992 and 2003; they found that there was no link between maternal obesity and prematurity. However, Su et al (2020) also conducted a retrospective study of Chinese women who delivered between 2015 and 2018; the authors concluded that there was an increased risk of premature birth with maternal obesity, recommending weight loss prior to conception. In summary, maternal obesity may be a predisposing factor to prematurity; in view of this, mothers-to-be should be encouraged to maintain a healthy weight.

Lack of antenatal care

Studies consistently show that women who receive early and regular antenatal care are less likely to have a preterm infant (Turienzo et al. 2016; Requejo et al. 2013). The health risks for women may increase during the pandemic due to a reluctance to attend visits in potentially crowded antenatal clinics or doctors' offices; particularly in countries that do not

impose and reinforce strict infection control measures (See Table 1) within their clinics. In addition, the indirect consequences of the pandemic can lead to reduced access to services due to an overwhelmed health system, a perceived lack of maternity services and the need for an increased focus on the reproductive needs of women during their childbearing years (Riley et al., 2020; Semaan A. et al., 2020).

Work related stress

Work related stress has been shown to be a risk factor for premature birth. In a recent literature review occupational stress was identified as a significant risk for premature birth (Takahata and Shiraishi, 2020). This stress is further increased if combined with socioeconomic disadvantage during pregnancy (Chen et al., 2020). Two recent publications have identified conflicting outcomes. The first, a literature review, identified that an increased risk of premature birth for women working fixed night shifts (21%), rotating shifts (13%) or longer hours (21%) (Cai et al. 2019). While in a study conducted in Brazil of 2416 women provided a counter view of the connection between workplace stress and standing for prolonged periods (Buen et al. 2020). It was found that women who do work and/or complete household chores unaided were less likely to have spontaneous premature births. Buen et al. (2020) suggest that their results need to be interpreted with caution.

Home related stress

Intimate partner violence or domestic violence (DV) is a risk factor for preterm birth and other adverse perinatal outcomes for the baby and mother (Donovan et al. 2016). Indeed, exposure to DV during pregnancy doubled the risk of preterm birth. Research into pregnancy and DV has found that between 3% and 9% of women experience abuse during pregnancy and higher rates of abuse occur with young maternal age, single relationship status, minority

race/ethnicity, and poverty (Alhusen et al, 2015; Tavoli et al., 2016). Direct physical assault to the abdomen and sexual abuse are associated with placental damage, uterine contractions, premature rupture of membranes, and genitourinary infections (Donovan et al., 2016). Many of the factors associated with DV are risk factors for preterm birth. Risk taking and unhealthy behaviours such as maternal smoking, alcohol or drug use, inadequate prenatal care, poor nutrition resulting in insufficient prenatal weight gain (Alhusen et al, 2015; O'Leary et al, 2009; Patra et al., 2011; Sanchez et al. 2013).

Pregnant women who are victims of DV tend to have higher levels of stress, less support from their partners, and lower self-esteem (Donovan et al 2016). The risk for preterm birth could be related to psychosocial, emotional and physical stress, depression, anxiety, isolation, decreased social support, and low self-esteem (Sanchez et al. 2013). Increased hypothalamic-pituitary-adrenal (HPA) is regarded as one important mechanism for observed associations between maternal psychiatric symptoms (anxiety disorders) and preterm delivery (Sanchez et al. 2013). Psychological stress can exacerbate pre-existing conditions such as hypertension and gestational diabetes increasing the risk of preterm birth (Wadhwa et al, 2011).

A disturbing aspect of the lockdown during COVID-19 is the pandemic coincided with the onset or escalation of domestic violence and abuse. Boxall et al. (2020) found that two-thirds of women who experienced physical or sexual violence by a current or former cohabiting partner since the start of the COVID-19 pandemic, said the violence had started or escalated. COVID-19 coincided with the onset of violence or coercive control for many women, and for others there was an increase in the frequency or severity of ongoing violence or abuse (Boxall et al., 2020).

Exposure to environmental pollutants

China suffers greatly from severe air pollution, and during COVID-19 China locked down one third of its cities to prevent the escalation of COVID-19 transmission. Lock down curtailed personal mobility and economic activities and led to significant improvement in air quality (He et al. 2020). Air pollution exposure has been reported to be a risk factor for preterm birth (Liu et al. 2019). Particulate matter (PM) is extremely small solid particles and liquid droplets suspended in air. It can be made up of a variety of components including nitrates, sulphates, organic chemicals, metals, soil or dust particles, and allergens. Particle pollution is released from motor vehicles, wood burning heaters, industry, bush fires and dust storms. The particle size is important and affects their potential to cause health problems. For example, PM10 (particles with a diameter of 10 micrometres or less), and PM2.5 (particles with a diameter of 2.5 micrometres or less). Both particle sizes are small enough to enter the lungs. Liu et al. (2019) found that the risks of preterm birth increase for each 10 $\mu g/m^3$ increase in $PM_{2.5}$, PM_{10} during the first trimester and in $PM_{2.5}$, PM_{10}, SO_2 (sulphur dioxide), O_3 (ozone) during the third trimester.

Recommendations

The modifiable risk factors of pregnancy need to be considered when pregnant women seek obstetric and/or midwifery care. While it is not possible to know why the number of premature babies may have decreased in certain countries during COVID-19, the importance of holistic antenatal care and fetal monitoring cannot be overstated. The pregnant woman and her partner also need to make informed decisions about ways to decrease the risks of preterm birth.

Influenza vaccination of pregnant women is associated with a decreased risk of adverse pregnancy outcomes including preterm birth (Fell et al. 2017) and confers effective

protection up to the age of 6 months for newborns whose mother was vaccinated during pregnancy (Bartolo et al. 2019). Campaigns directed at pregnant women to be vaccinated against influenza are needed. Bartolo et al. (2019) found that 35.5% of the 2045 pregnant women in their study reported they had been vaccinated against influenza during their pregnancy; the factor significantly associated with vaccination uptake was previous influenza vaccination. Other influences included, to a lesser degree, were first pregnancy, history of preterm birth, the mother's knowledge of the influenza vaccine (and the perception that complications associated with the vaccine were low). Health professionals need to advocate for the influenza vaccination because Bartolo et al. (2019) found that health care worker vaccination recommendations, evidence-based information and hospital-based prenatal care in the first trimester of pregnancy were positively associated with vaccine uptake by pregnant women. Indeed, the primary motivating factor was protecting the baby against influenza.

The nutrition of pregnant women needs careful consideration. Eating foods that contain prebiotics and probiotics should be encouraged. Probiotic supplementation, at this stage, does not seem to pose safety risks for pregnant women and is not associated with an increase in adverse outcomes (Buggio et al. 2019; Nordqvist et al. 2018; Elias et al. 2011). Recognizing and treating the women having urogenital infections, when it has not become clinically evident, will decrease the percentage of women going into preterm labour and will improve the perinatal outcome (Verma et al., 2014). In order to decrease the impact of periodontal disease on preterm birth incidence, the promotion of pre-pregnancy oral health is recommended. For those women who are already pregnant, early diagnosis, treatment and monitoring is essential. It is noteworthy that most of the research has shown that periodontal treatment is safe for pregnant women and can improve periodontal status (Huck et al. 2011). It is not yet known if the treatment of periodontal disease reduces the risk of preterm birth (Polyzos et al. 2010).

In summary, the work of Been et al (2020), Hedermann et al. (2020b) and Philip et al (2020) suggest a possible link between the modifiable risks of pregnancy and the lockdown necessitating pregnant women stay at home. Decreasing contact with others associated with physical distancing, such as on a daily commute may have resulted in less infection. A focus on hygiene could have also decreased the risk of infections. Lockdown could have meant better nutrition with more home cooking and less take-away or less nutritious food, perhaps leading to a more normal pregnancy weight gain. In some countries, exercise was an approved reason to leave the house. Avoidance of people outside the house could have meant less access to tobacco and illegal drugs and less opportunity for unprotected intercourse resulting in sexually transmitted diseases. Less work stress could have resulted in improved sleep, however financial stress could be an issue. Fewer industries that spill pollutants into the air could have resulted in less air pollution. While at this stage it is not possible to make firm conclusions from these studies' findings, considering the points raised in this paper can generate useful discussion and knowledge for learning.

CONCLUSION

COVID-19 and the work of Philip et al (2020), Hedermann et al. (2020a, b) and Been et al (2020) has provided the opportunity to examine the modifiable risks for preterm birth. It is unlikely that this opportunity will present again because pregnant women will in all probability choose not to isolate at home with all the restrictions imposed during the initial lockdown. Health professionals who care for pregnant women need to address the modifiable risk factors for preterm birth as part of their mother and baby surveillance. Decreasing the number of preterm births by paying attention to the modifiable risk factors is considered a major public health initiative and essential to optimise outcomes of our vulnerable premature babies and families.

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