Chapter

Prediction of Caesarean Delivery

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Abstract

For expectant parents, a first birth is notable for its unpredictability, and the path to safe labour and delivery is commonly complicated by a requirement for unplanned caesarean delivery. The ability to anticipate an uncomplicated vaginal birth, or to predict the requirement for unplanned caesarean delivery, carries the potential to facilitate optimal birth choices. For example, elective caesarean delivery confers substantially less risk than unplanned caesarean delivery performed during the course of labour. Pre-delivery knowledge of a high predictive risk of requiring intrapartum caesarean delivery could lead to women opting to deliver by elective caesarean delivery, thereby lowering associated risks. Equally, pre-labour knowledge of a high prospect of achieving a successful and uncomplicated vaginal birth could result in enhanced motivation for women to deliver in a less medicalised environment. Predictive risk models have been utilised to good effect in other areas of medicine. The incorporation of a risk predictive tool for intrapartum caesarean delivery would enable women and their caregivers to choose the most appropriate management plan for each woman.

Keywords: prediction model, caesarean delivery, personalised care

1. Introduction

The last three decades have witnessed an escalation in global Caesarean section rates. It is well recognised that there is an association between delivery by Caesarean section and both short and long-term maternal morbidity, particularly at an advanced stage in labour [1]. This association is significantly stronger in the setting of emergency Caesarean section than scheduled elective non-labour Caesarean delivery.

It is notable that post-operative complications, including haemorrhage and perioperative infection in women who undergo unplanned Caesarean delivery are significantly higher when compared to women who undergo elective Caesarean delivery [2].

Magann et al. [3] examined the outcomes regarding post-partum haemorrhage of over 4000 Caesarean section deliveries in Australia in their observational study. They determined that the incidence of post-partum haemorrhage in an emergency setting was 6.75% and the incidence in an elective setting was 4.74%.

A 2014 Cochrane review [4] examined the rates of post-partum sepsis for both intrapartum and elective caesarean sections. They identified 95 studies, which recruited over 15,000 women. They determined that the rates of wound infection were 9.7 and 6.8% respectively. As regards endometritis, the rates were 18.4% for intrapartum caesarean sections versus 3.9% for elective caesarean sections.

It is important to also reference the association in particular between intrapartum caesarean sections and maternal morbidity. The incidence of caesarean sections performed at full dilatation is increasing [5]. These deliveries are associated with an increase in maternal morbidity including visceral trauma, haemorrhage and extension of the wound [6].

The Archives of Obstetrics and Gynaecology published a review in 2017 which specifically aimed to enumerate the differences in complications experienced in women who underwent elective Caesarean delivery and those who underwent emergency Caesarean delivery [7].

This systematic review included nine individual studies. Inclusion criteria dictated that the studies had to be either a randomised control trial study or a controlled clinical trial study to perform a comparison of the morbidity and mortality between elective and emergency intrapartum Caesarean delivery.

The combined results demonstrated that the rates of infection, fever, urinary tract infection, wound dehiscence, disseminated intravascular coagulopathy, and reoperation of emergency Caesarean section were all much higher than those of elective Caesarean section.

A unifying sentiment that can dominate a woman's post-natal course after an intrapartum Caesarean section delivery is the desire to anticipate this intervention. Prenatal knowledge that a successful vaginal birth will not be achieved would obviate the labour-associated risks that frequently result in maternal or perinatal morbidity, and the dissatisfaction of having undergone a 'trial' of labour to no avail.

The Organisation for Economic Co-Operation and Development (OECD) reports that there has been a significant increase in Caesarean section delivery rates in most OECD countries between the years 2000 and 2015. The average rate has increased from 20 to 28%, although there does appear to have been a slow-down in the rate of growth in the past 5 years [8]. It is also notable that different hospitals and regions within the same country can show significant variation in their Caesarean section rates. For example, Italy continues to show huge variation in the Caesarean delivery rates. High rates of Caesarean delivery appear to be driven by the southern region. Similar variations in rates between different regions are also observed in Spain [9].

Of note, the U.S. has shown a decline in its Caesarean delivery rate for the fourth consecutive year. Caesarean delivery rates in 2016 were 31.9%, which had fallen slightly from 32% in 2015. Prior to this, they had increased annually from 20.7% in 1996 to a peak of 32.95 in 2009 [10].

On a global level, the Caesarean section rate over the past 30 years has escalated but interestingly, no associated significant maternal or perinatal benefits have been demonstrated [11–13].

This increase prompted The Lancet to compile a series on optimising the use of Caesarean section, which was published in October 2018. The authors of this review argued that the decision to perform a Caesarean section might be guided by the psychological or clinical needs of the mother, the clinical needs of the baby or by a combination of both [14].

However, where rates of Caesarean section exceed what is considered a 'recommended rate' of 10–15% as per the World Health Organisation [15], there were three main drivers identified which were though to contribute to perceived over-use of this intervention. These were categorised broadly as health professionals; communities (incorporating families, childbearing women and the broader society) and health care systems (comprising organisational design and cultures and financing).

As regards communities, families, childbearing women and the broader society, it was noted that women worldwide would not prefer to have a Caesarean section without a significant maternal or foetal indication [16]. This is in direct contrast to

the common perception that many women would choose a Caesarean section as a matter of preference [17].

Factors relating to health professionals highlighted that being male, being employed in a university-affiliated hospital and a fear of litigation were associated with an increased likelihood of an obstetrician performing a Caesarean section [14]. They also found Caesarean section might sometimes be used for convenience. This was particularly noted where both a combination of private and public work was performed in the same unit. The scheduling of elective Caesarean sections can allow commitments to public work being fulfilled while allowing the performance of private work on the same premises [18].

Of particular interest to clinicians is addressing the safe prevention of unwarranted primary Caesarean section delivery. In March 2014, a joint consensus was issued by the Society for Maternal Fetal Medicine and American College of Obstetricians and Gynaecologists (ACOG). This addressed the importance of the safe prevention of primary Caesarean delivery and this was reaffirmed in 2016 [19]. As previously mentioned, The Lancet has also highlighted the importance of addressing appropriate and safe use of Caesarean section in order to address the escalating rates worldwide [9].

This chapter will deal with the use of prediction models in medicine in order to address how best to antenatally predict the need for an intrapartum Caesarean section for a nulliparous woman. The clinical application of such a prediction model would ultimately be that those women issued with a high likelihood for intrapartum Caesarean delivery might opt for an elective Caesarean section with the associated decreased morbidity risks.

On a corollary to this is the point that many women would likely prefer the prospect of a trial of labour if they were assigned a low-risk for intrapartum caesarean delivery. Furthermore, this may allow women the opportunity to consider a less medicalised environment for birth for example in a midwifery-led unit. A review of the literature would suggest that the majority of women would opt for a vaginal delivery over a caesarean section. An Australian study which asked women to complete an antenatal questionnaire found that 93.5% of women would prefer a vaginal delivery over a caesarean section [20]. This showed very similar results to a Swedish-based study which found that only 8.2% of nulliparous women would prefer to deliver by caesarean section [21]. Similar opinions were also found amongst women in Brazil and Chile, which are countries with traditionally high caesarean section rates [22–24]. The Genesis risk prediction model could empower women entering labour with a low predictive risk score for an intrapartum caesarean section that they had a high likelihood of a desirable successful vaginal delivery.

I will outline the development and usage of prediction models in other areas of medicine and the research into various factors, which have been highlighted as predictive for Caesarean delivery. If achievable, the ability to predict the outcome of an attempt at first labour is highly desirable. It is apparent that the safe prevention of primary Caesarean delivery is an outcome, which would be welcomed by the international obstetric community.

2. Predictive models

2.1 Rationale for use of predictive models in healthcare

Certain decisions in healthcare require a detailed process in order to provide optimal care to patients. This can be complicated by a deficit in standardisation of processes, which aim to encompass the needs of multiple stakeholders.

Various modelling tools can assist the decision-making process. Some of these aim to predict a clinical outcome, whereas others focus on identifying the patients who may be most at risk of developing a certain condition [25].

These tools are created using formulae that may assist in decision-making. These in turn can assist in resource planning and allocation in healthcare. Examples of such tools are prognostic and prediction models [26].

Prognostic models may have varied uses, including 'guiding healthcare policy by generating global prediction scenarios; determining study eligibility of patients for new treatments; selecting appropriate tests and therapies in individual patient management including supporting decisions on withholding or withdrawing therapy' [27].

The two main types of prognostic models seen in practice are those at the individual patient level and those at the patient population level. Individual patient models are used in suggesting advice for treatment and to provide consultation, which is patient-centered. Patient population models are more focused on the identification of discrepancies and trends amongst patient groups for a specific criterion [27].

Predictive modelling can be used to help identity patients who may be at high-risk for a certain outcome, e.g. an intrapartum Caesarean delivery. Predictive modelling can also be used in order to manage healthcare resources by initiating appropriate interventions to prevent high-cost outcomes [28].

One such example which has been developed in clinical practice is the cardiovascular disease risk assessment for primary prevention. The Framingham Heart Study looked at 7733 participants who had initially been free of coronary heart disease and were aged between 40 and 79 years. They found that the lifetime risk of being affected by coronary heart disease (CHD) for these participants by age 40 was 32% in women and 49% in men [29].

This highlighted the importance of cardiovascular disease risk assessment being performed from the age of 20 years of age or from a person's first encounter with the healthcare system. This can then in turn predict those individuals who are at the most significant risk of cardiovascular disease. Identifiable risk factors included cigarette smoking, hypertension, diabetes mellitus, premature family history of cardiovascular disease, chronic kidney disease and obesity. These individuals can then be commenced on appropriate primary preventive therapies or receive alternative appropriate intervention. Predictive modelling acts on the basis of taking a proactive approach, i.e. the identification of trends and forecasting of events which may cause implications for stakeholders in healthcare [25].

There are several factors which need to be considered in the implementation of a new prediction model [30]. These include:

- The creation of a focus on the population as a whole and examining all aspects of healthcare
- An emphasis on change of behaviour in the longer-term
- The utilisation of data to create programs which aim to address learning, health status and individualised risk
- The development of health plan designs which act to support and incentivise

Providers of healthcare and patients are both motivated to achieve improved outcomes and this suggests that the use of these models is likely to increase with the added benefit of potential reduction in healthcare costs.

For our purposes, accurate prediction of Caesarean delivery may allow consideration being given to elective Caesarean delivery in the event of a woman being considered high risk for an intrapartum Caesarean delivery in order to reduce the incidence of specific maternal morbidities as aforementioned including infection, haemorrhage and the need for a repeat surgery. A low predictive risk score also empowers women who are keen on a successful vaginal delivery with the knowledge that they have a high likelihood of achieving same.

2.2 Use of predictive models in obstetrics

Historically, the field of obstetrics has been successful in developing prediction models but has been poor in fully validating and thus implementing them effectively [31].

On a daily basis, we still use two examples of prognostic models in obstetrics, which were developed over 60 years ago. One such model is the Apgar score, which assesses newborn babies immediately after their birth. The other model is the Bishop score, which assesses the status of the cervix before and during induction of labour [32, 33]. Both of these models were developed in the 1950s–1960s and are still used clinically, likely due to their ease of use and continued relevance [31].

The Apgar score was re-examined and re-validated by a research group in Texas almost 50 years after its initial introduction. They reviewed the charts of more than 150,000 deliveries over a 10 years period and found there was a significant correlation between these babies' 5 minute Apgar scores and neonatal mortality [34]. This score remains an easy and quick way to determine if resuscitation has been effective and has therefore survived the test of time [35].

The Bishop score assesses cervical dilatation, cervical effacement, cervical consistency, cervical position and foetal station. A higher score meant a woman was more likely to have a spontaneous onset of labour sooner. It is still in use today and can aid clinicians in deciding the most appropriate method of delivery for each woman. The work of Professors Apgar and Bishop essentially formed some of our earliest prediction models in obstetrics.

Only two thirds of the papers [62.4%, 164/263] in a large systematic review of prognostic models in obstetrics were found to have presented their models in such a way that external validation would be feasible [31]. This has been highlighted as a concern given the importance of validity in the development of such models.

Certain models can be too complex for routine clinical usage and this may lead to a reluctance on the part of the clinicians to accept them [36]. For example, the use of an electronic program to help predict those patients most in need of requiring an influenza vaccination was found to be ineffective as it did not prove to be user-friendly. It is also important that models which have been developed are also validated in a new population as otherwise it may not be possible to generalise them to a different cohort of patients [37]. This is also known as impact analysis and this paper by Reilly et al. highlights that very few prediction models have undergone formal impact analysis or validation. This is essential in order for clinicians to know if the usage of such a model will have a positive or negative effect, i.e. is there a possibility that it will cause harm. The authors highlighted the benefit of having clinicians involved in the development and validation of such models before, during and after implementation.

There are limitations to the development and use of prediction models in obstetrics. It has been shown that internal validation is largely successful and the models have been shown to perform well under this setting. However, there has been a deficit of research into looking in to externally validating these prediction models in a different cohort. Another limiting factor for clinical usage and

which was discussed in a commentary in the British Journal of Obstetrics and Gynaecology (BJOG) in 2016 is how interventions might be handled in a prediction model [38]. This commentary highlighted the issues, which face clinicians in validating obstetric prediction models in order to effectively implement them in clinical practice. They specifically examined the area of pre-eclampsia and noted that a phenomenon described as the treatment paradox can occur; a strong predictor of a common complication may trigger an effective treatment (e.g. commencement of anti-hypertensive therapy) at an early stage and this will then prevent the occurrence of a certain proportion of adverse outcomes. This may result in the predictor, which triggered the treatment initially appearing poorer in its predictive performance [39, 40].

The BJOG review [38] further examined a prediction model which has been successfully validated for the predicting pre-eclampsia (PREP model-Development and validation of Prediction models for Risks of complications in Early-onset Pre-eclampsia) [41] in order to ascertain what made it a successful process and highlighted certain factors which can aid validation. These included large sample size, standardisation of treatment or intervention, and the consideration to the initiation of treatment being an outcome itself, i.e. 'When starting a treatment is likely to prevent an adverse outcome, those who received the treatment could also be considered to have experienced the outcome'. These factors may aid obstetricians in validation of prediction models going forward and in handling the treatment paradox.

2.3 Use of predictive models in gynaecology

The field of gynaecology has also developed a new risk prediction model in recent times. A large cross-sectional international cohort study involved the participation of 5020 patients from 22 centres [42]. This study developed and validated a risk prediction model to predict the risk of malignancy in adnexal masses using specific ultrasound features which are defined in the simple rules.

In 2008, the simple rules were described by the International Ovarian Tumour Analysis (IOTA) group [43]. These specific ultrasound features are known as either B-features (where tumours are likely benign) or M-features (where tumours are likely malignant).

In using the simple rules, and there are no specific features identified or if there is a conflict between the features, then the rules cannot be applied and the result is inconclusive. In this instance, it is recommended to classify the findings as having a higher risk of malignancy in order to increase the sensitivity for ovarian cancer [33].

The simple rules have been well received by clinicians and adopted by international bodies such as the Royal College of Obstetricians and Gynaecologists [34]. Zimmerman et al. aimed to develop and validate a model based on the criteria laid down in the simple rules. When used as originally suggested, the simple rules aimed to categorise tumours as belonging to one of three distinct groups: benign, malignant, or inconclusive. Zimmerman et al. demonstrated that the simple rules could also be used to estimate the risk of malignancy in every adnexal mass. In this way, they can be applied to individual patients to optimise their own management [31]. The rules were found to be applicable in 76% (386/507) of the tumours, with a sensitivity of 95% (106/112) and a specificity of 91% (249/274). This risk prediction model has the potential to be broadly accepted given its ease of use and the fact that it is based on standards which have already been accepted and are used by the gynaecological community. Several follow up studies [35, 36] have highlighted that the rules can be easily utilised by ultrasonographers and that the protocol can be an accurate test to diagnose ovarian cancer.

2.4 Use of predictive models in other aspects of health care

Increasingly, attempts have been made to develop and validate prediction tools which aim to predict the risk of hospital readmission [44]. Interest in this area has evolved for a number of reasons. Of clinical importance is that an intervention while a patient remains in hospital may help to reduce readmission rates as those in need of additional care may receive it while still an inpatient. It also helps to target delivery of interventions which are resource-intensive to those with the greatest need [45]. This would result in a stratification of the risk of readmission, which may hold clinical relevance. In turn, this would allow for early information during a patient's admission, which would allow the initiation of an intervention such as advanced discharge planning which could begin during the admission and before discharge from hospital. Models used should be accurate, clinically relevant, use easily obtainable data and be able to be used in large patient populations [46].

Covariates are used in risk prediction models. This is done with the aim of detecting a given outcome or to determine a defined period of time whereby an individual is thought to experience a specific outcome [47].

These predictors are varied and may encompass characteristics such as gender or age, biochemical markers, coronary artery deposits or specific genetic markers [48].

In the field of cardiology, prediction models include Framingham [49], SCORE [50], ASSIGN [51], EUROSCORE [52], PROCAM [53], and Wells' scores [54].

Prediction models may assist individuals and their clinicians in deciding the most appropriate management plan or on the implementation or withholding of treatment or lifestyle interventions.

There is an increased desire to implement personalised care and because of this, research into prediction models is increasing [55]. In the current era of risk-tailored and personalised cardiovascular care, studies on prediction models are abundant. A recent statement of the American Heart Association on criteria for the phased evaluation of markers of cardiovascular risk underlines this. A key term in this statement was that 'multivariable prediction models and cardiovascular markers should not (simply) be evaluated in isolation for their prediction abilities but rather on their added prediction contribution beyond existing or established predictors requiring a multivariable approach in design, conduct, analyses and reporting' [56].

It is important that the development of prediction models should follow strict methodologic processes. New prediction models should detail their development process and highlight all their statistical calculations in order to allow researchers in the future to reproduce and validate their findings. Research into the relatively new field of biomarkers needs to determine their additional benefit to pre-existing models [57].

The selection of specific chemotherapy regimens is made based on examination of the outcomes for specific subtypes and specific types of malignant tumours, their likelihood to progress to metastases and their overall prognosis [58, 59]. The overall effectiveness of certain agents also means that the development of tiered strategies has developed in order to overcome variations seen in the resistance of certain tumours [60].

This study examined the responses of chemotherapy agents cisplatin, carboplatin and oxaliplatin with certain gene signatures [61]. This group developed a machine-learning based prediction model, which aimed to predict the effectiveness of the agents above to certain gene signatures. This tailored treatment may result in an improved treatment response to an individual's specific cancer biology which may result in reduced treatment duration or the minimum usage of chemotherapy agents to achieve a desired response [62].

Cancer treatment is challenging as the disease can be complicated by genetic heterogeneity with differences in the genetic composition of tumours causing different responses to treatment [63].

The impact of this variance in genetic composition means that there may varied responses to treatment regimes. This means that the therapy may only benefit a small proportion of the patients treated [64]. In order to minimise the associated adverse effects which can occur with using these treatments, it is of particular benefit to patients with cancer to decide on the optimal treatment regime at the time of diagnosis [65].

Ubels et al. [65] developed the idea of simulated treatment learning (STL). This program assists in identifying the factors that can best predict treatment benefit and can be applied to gene expression datasets with two treatment arms and associated survival data. It works by identifying genetic similarities between patients from different groups to model how a particular patient would respond to an alternative treatment plan and is defined based on the expression of the genes in the tumour. Their work focused on patients with multiple myeloma and how best to predict the benefit of treatment. Multiple myeloma affects the bone marrow by causing abnormal multiplication of the plasma cells. The typical median survival is approximately 5 years [66]. Multiple myeloma is one of the known conditions where a difference in gene expression profiles is observed amongst patients [67]. This variation in genes expression means that identification of individual genetic signatures may be useful to help predict those who would benefit from STL.

3. Prediction of intrapartum caesarean section

3.1 Definition of intrapartum caesarean section

An intrapartum Caesarean section is a Caesarean section, which occurs during the course of labour. According to the American College of Obstetricians and Gynaecology, the most common indications for primary Caesarean delivery include, in order of frequency, labour dystocia, abnormal foetal heart rate tracing, foetal malpresentation, multiple gestation, and suspected foetal macrosomia [19].

3.2 Labour dystocia and associated risk factors

The progression of labour and recognition of prolonged labour can heavily influence the management of labour and the need for intrapartum Caesarean section. Prolonged labour has been defined as true labour dystocia and may be caused by either obstruction of labour or contractions, which are inadequate in number or strength. Prolonged labour is the main indication for performing an intrapartum Caesarean section in nulliparous patients [68].

Labour dystocia may be recognised in either the first or the second stage of labour. It has been reported to affect 21–37% of nulliparous women and 2–8% of multiparous women [69–71]. It has been attributed to several factors including macrosomia, reduced capacity of the pelvis, inefficient uterine contractions or a combination of these factors [72]. There are multiple studies in the literature examining the causes of labour dystocia.

The association between foetal macrosomia and labour dystocia is well described. Galvin et al. have previously looked at the accuracy of antenatal detection of macrosomia >4000 g and subsequent delivery outcomes in the absence of antenatal intervention [73]. They noted ultrasound sensitivity and specificity of 41.2 and 94.1% respectively for detecting macrosomia >4000 g. The positive predictive value (PPV)

and negative predictive value (NPV) were 57.5 and 89.1% respectively. Their conclusion was that the capacity of ultrasound to detect foetal macrosomia is limited.

This finding is also reflected in a study by Chuahan et al. [74]. This group conducted a review of international articles from studies containing a sample size of at least 1000 cases in order to determine the prevalence and accuracy of determining macrosomia. The probability of detecting a macrosomic baby in a term, low-risk baby is ranged from 15 to 79% sonographically and 40–52% with clinical examination. They determined that the detection of macrosomia is reliable sonographically and clinically if the incidence of macrosomia is at least 20% in the relevant cohort.

The influence of foetal head circumference on delivery outcome has been extensively studied. Kennelly et al. suggested in 2003 that foetal head circumference >37 cm is a good predictor of prolonged labour in their study which examined 423 nulliparous women with a singleton cephalic presentation who had a spontaneous onset of labour [75]. They determined that as birth weight and foetal head circumference increased, there was an associated increase in mean duration of labour, duration of second stage of labour and usage of oxytocin ($P < 0.001$).

Elvander et al. conducted a population based register study, which was published in 2011 [76]. This examined a total of 265,456 singleton term neonates who were born to nulliparous women between 1999 and 2008 in Sweden. This data was extrapolated following analysis of the Swedish Medical Birth Register. The investigators examined factors including labour dystocia, instrumental delivery, foetal distress and Caesarean section. They found that the prevalence of each outcome increased as the circumference of the foetal head increased. In the case of Caesarean section in particular, the odds ratio was 1.22 (95% CI 1.04–1.42), indicating that a large foetal head (39–41 cm) is associated with labour dystocia and subsequent intrapartum Caesarean section. Valsky et al. also highlighted prolonged second stage of labour (greater than 110 minutes) and increasing foetal head circumference as risk factors for obstetric anal sphincter injury in nulliparous women. They showed through logistic regression that a head circumference greater than 35.5 cm and a second stage of labour greater than 110 minutes increased the odds of obstetric anal sphincter injury by a factor of 5.32 [77].

The position of the foetal head has also been extensively examined as a risk factor for Caesarean section. Occipito-posterior position is identified in approximately 15–20% of women before labour at term [78, 79]. The majority 90–95% undergo rotation during labour to an occipito-anterior position [80, 81]. The presence of an occipito-posterior position at delivery has been extensively examined with respect to maternal morbidity and an increased risk for Caesarean delivery [82–85].

Maternal age has been strongly associated with delivery by Caesarean section. Women aged 40 and over are more than twice as likely to deliver by Caesarean as women under age 20 [8]. Advanced maternal age has been shown to be associated with an increased risk of obesity [86], diabetes and hypertensive disease [87–89] and interventions including delivery by Caesarean section [90–94]. There is evidence demonstrating that the rate of Caesarean sections performed on an elective basis in the absence of a strong medical indication increases with advancing maternal age [95, 96]. Maternal age has also been shown to be an independent risk factor for Caesarean delivery [97].

Maternal BMI has also been associated with delivery by Caesarean section. Young and Woodmansee in 2003 published the results of an 8-year review of women who delivered in their practice. They found that primiparous woman who had a BMI of over >30 kg/m^2 were six times more likely to undergo an intrapartum Caesarean delivery for labour dystocia than those primiparous women whose BMI was <20 kg/m^2. This difference in mode of delivery persisted even when results were controlled for gestational age, birth weight, maternal height and maternal age [98].

Algovik et al. performed a retrospective analysis of the Swedish Birth Registry and identified 104 women in 47 families where at least two of sisters had undergone intrapartum Caesarean delivery at term attributed to labour dystocia during the course of a first labour [72]. A genetic basis for labour dystocia was sought, which identified strong evidence of linkage at chromosome 12p12 and at five other separate loci, which may of significance. There was no specific prevalence data included in their report. The authors however were unable to identify a specific gene, which may be responsible for labour dystocia. Re-sequencing of oxytocin (OXT) and oxytocin receptor (OXTR) seemed to be obvious candidate genes for this analysis. However, they did not allow for identification of any potential causal mutations. Further studies with a larger study population were recommended.

Mittal et al. [99] have also performed genetic testing to establish a cause for arrest of labour. They obtained myometrium samples from 50 women who underwent primary Caesarean delivery in a prospective study. All of these women had had a spontaneous onset of labour. They compared two groups of women. One group (n = 29) underwent Caesarean delivery due to either non-reassuring foetal status or foetal malpresentation. The second group (n = 21) underwent Caesarean delivery due to an arrest of labour. This was defined as women who had complete cervical dilatation but without continued foetal descent for greater than 1 hour. They identified over 400 different genes, which differed in women who experience an arrest in the descent of the foetal head during labour when compared with those who underwent Caesarean delivery for non-reassuring foetal status or foetal malpresentation. An over expression of certain inflammatory and biomarkers was identified in women who experience an arrest of descent including hypoxia inducible factor-1a, prostaglandin-endoperoxidase synthase 2 and interleukin-6. These factors were identified using micro-array. The authors did acknowledge that their study may be limited, as they could not establish a true causative effect, as this would require studies involving serial sampling in women, which would not be feasible. However, they recommended that this study may act as a framework for additional studies, which may address potential therapeutic interventions.

3.3 Model of care as a predictor of caesarean section rates

In many maternity settings worldwide, women can opt for obstetric or midwifery-led care. A descriptive comparative Australian study examined the outcomes of women who opted for either midwifery-led care or standard hospital care, which incorporated more input from the obstetric team. The study found that more women who opted for midwifery-led care were very satisfied with their overall care during their pregnancy, labour and delivery than those who experienced standard hospital care (80% very satisfied versus 53.2%). However, the study found that there was no observable difference in the Caesarean delivery rate between the two groups [100].

A randomised controlled trial, also based in Australia, examined if there was a difference in the Caesarean delivery rate between women who were assigned standard hospital-based care or community led care. However, this study differed from the aforementioned descriptive study in that those who experienced community led care were under the joint collaborative care of both midwives and obstetricians. In this study, there was a significant difference in the Caesarean delivery rate between the two groups. The group that experienced community based care had a Caesarean section rate of 13.3% (73/550) and the group that had standard hospital based care had a Caesarean section rate of 17.8% (96/539). The difference remained after controls were implemented for other known factors which may have contributed to their Caesarean sections (OR = 0.6, 95% CI 0.4–0.9, P = 0.02) [101].

A Canadian randomised controlled trial in 1996 examined the outcomes of nearly 200 low-risk women who were assigned randomly to either nurse-midwife led care or physician (family doctor and obstetrician) led care. The nurse-midwife led group had a Caesarean deliver rate of 4% in comparison with 15.1% in the physician group. There were also lower rates of epidural and episiotomy usage in the nurse-midwife led group [102].

Their relatively low numbers may explain the variations in the reported findings of these studies. The British Journal of Obstetrics and Gynaecology performed a systematic review in 2005 of randomised controlled trials in which the study intervention was characterised as midwifery-led care versus standard obstetric care. This review highlighted seven trials, including 9148 women. In general, they found that women who experienced midwifery-led care in their antenatal and labour courses were less likely to have interventions in labour including induction of labour, use of oxytocin, epidural usage, CTG monitoring, operative vaginal delivery and episiotomy. However there was no difference in the Caesarean delivery rate between the two groups (OR 0.91; 95% CI 0.78–1.05) and there were no observable differences in infant and maternal outcomes. [103].

The British Journal of Obstetrics and Gynaecology published the 'Birthplace study' in 2011 [104]. This large prospective cohort-based study of 64,538 women had the objective of comparing perinatal outcomes, maternal outcomes and interventions in labour by planned place of birth at the start of care in labour for women with low risk pregnancies. This study took place in NHS care facilities across England. Recruitment criteria included both nulliparous and multiparous women. The Birthplace study concluded that a choice of birth setting was optimal for women with low risk pregnancies and determined that those women who delivered in a midwifery unit or multiparous women who delivered at home experienced fewer interventions with no change in perinatal outcomes. When specifically comparing intrapartum Caesarean section rates, intended place of birth (with this decision made antenatally) varied significantly. Those who intended to give birth in an obstetric unit had an intrapartum Caesarean section rate of 11.1% (99% CI 9.5–13.0). This compared with those who intended to give birth in a midwifery unit or at home having intrapartum caesarean delivery rates of 3.5% (99% CI 2.8–4.2) and 2.8% (99% CI 2.3–3.4) respectively.

3.4 External pelvimetry

It is estimated that 600,000 worldwide die annually as a result of complications of pregnancy [105]. Of these, approximately 25% are thought to be attributable to cephalo-pelvic disproportion [105–108]. Cephalopelvic disproportion is defined as a mismatch between the size of the foetal head and size of the maternal pelvis, resulting in 'failure to progress' in labour for mechanical reasons [109]. It is therefore of significant global public health benefit to be able to accurately predict and detect these women who are more likely to require Caesarean section and to be in a position to predict this prior to labour onset. This is of particular importance in areas where Caesarean section is not feasible in order to be able to refer these women to units where Caesarean section may be performed. In the developed world where access to Caesarean section is easier, it is also desirable to be in a position to accurately predict those women who may require same, thus the importance of development of prediction models for Caesarean section.

External pelvimetry was the first known technique used to predict cephalopelvic disproportion [110, 111]. It involves the usage of a pelvimeter (e.g. Breisky pelvimeter). August Briesky was an Austrian gynaecologist who developed a pelvimeter in the nineteenth century in order to aim to accurately measure the dimensions of

the female pelvis. A prospective cohort study published in the British Journal of Obstetrics and Gynaecology in 2000 by Liselele et al. [110] outlined the findings of 605 nulliparous women carried out in four hospitals in Zaire. They assessed maternal height and pelvimetry at the third trimester antenatal visit in order to predict women at risk for cephalo-pelvic disproportion with subsequent increased risk of Caesarean section. They considered women with a height less than 150 cm and/or external pelvic distances less than the 10th centile (<9.5 cm) for the population to be at highest risk. A height gauge was used to ascertain maternal height and pelvimetry was assessed externally using a Breisky pelvimeter. They considered cephalopelvic disproportion to be present in 42 women. Their analysis showed that maternal height less than 150 cm and/or transverse diagonal of the Michaelis sacral rhomboid area less than 9.5 cm were most likely to be associated with cephalopelvic disproportion and labour dystocia (odds ratio of 2.2 [95% CI 0.9–5.4] and 6.5 [95% CI 3.2–13.2], respectively]. They also showed a positive predictive value of 24% [95% CI 2–8 to 5–8]) [110]. The transverse diagonal of the Michaelis sacral rhomboid area assessed by pelvimetry was noted to be of significant importance in the development of a model. The authors of this study recommended external validation of this model in a separate cohort before it becomes implemented in clinical practice. With a PPV of 24% this did not translate into a worthy research pursuit in high resource income setting. However, it is worth considering in the low resource setting where timely access to skilled birth attendants may be considerably restricted.

In 2007, Rozenholc et al. [112] performed another prospective cohort study specifically incorporating the measurement of the transverse diagonal of the Michaelis sacral rhomboid area which had been noted to be predictive by Liselele et al. previously, along with other anthropometic measurements including maternal height. This study looked at 807 nulliparous term women at term who completed a trial of labour and delivered a singleton fetus with a cephalic presentation. Ninety-eight women (12.1%) were found to have labour dystocia. They concluded the combination of the maternal height with the transverse diagonal of the Michaelis sacral rhomboid area could identify, before labour, more than half of the cases of dystocia in nulliparous women, therefore being a useful prediction model for prediction of Caesarean section.

3.5 X-ray pelvimetry

X-ray can also be used to assess pelvimetry. This is usually done by measuring the pelvic outlet, pelvic inlet and mid-pelvis using conventional x-rays with an anterior-posterior and a lateral view [113]. A Cochrane review published in 2017 identified a total of 1159 women who had participated in five separate trials. All five of these trials used X-ray pelvimetry in pregnancy [114]. This review found that there was insufficient evidence to support the routine use of X-ray pelvimetry for assisting with decision making in determining the most appropriate mode of delivery for women. They concluded that women who underwent an X-ray pelvimetry may have an increased likelihood of undergoing a Caesarean section without any improved benefits for the woman or baby.

3.6 MRI pelvimetry

The usage of MRI has now been applied to pelvimetry. This has potential advantages including the fact that there is no exposure of mother or fetus to radiation and the higher calibre of the quality of images makes it easier to calculate the volume of the maternal pelvis and the foetal head [115].

Sporri et al. in their prospective observational study published in 2002 also determined that the efficacy of MRI for clinical use in dystocia is limited and recommended further research in order to determine the most appreciate anatomical landmarks which should be examined [116].

In 2004, Zaretsky et al. published their findings on MRI assessment of pelvimetry and its usage in the prediction of labour dystocia in another prospective study. This involved performing an MRI on 101 nulliparous women who were scheduled for an induction of labour for post-term pregnancy (>42 weeks). They found that MRI is accurate at predicting women who are at significant risk for labour dystocia but it is not of significant benefit when compared with other methods of pelvimetry [117].

3.7 Models for predicting vaginal birth after caesarean section

There is a significant body of research, which has examined the ability to predict a successful vaginal birth after a previous Caesarean section (VBAC).

The National institute of Child Health and Human Development Maternal-Fetal Medicine Units Network created a registry between 1999 and 2002 that incorporated the pregnancy outcomes of women who delivered at their 19 units. Using this data, a prediction model was developed to provide individual risk of probability of a successful VBAC for women with a singleton, cephalic presentation fetus at term who had experienced one prior Caesarean section. The data of 11,856 women were analysed. The key predictors include maternal BMI, maternal age, body mass index, ethnicity (Caucasian women having higher success rates), timing of the vaginal delivery in relation to the Caesarean, history of vaginal delivery and indication for the prior Caesarean [118].

The model has been successfully validated by this group and in several other cohorts [119–121].

3.8 Conjugate models to predict labour dystocia

Kim et al. in their prospective observational study published in 2010 examined clinical and ultrasonographic parameters for predicting the risk of intrapartum Caesarean delivery in nulliparous women [122].

These investigators recruited 453 women and performed clinical and ultrasonographic assessments at 37 weeks' gestation. Fifty-seven (12.6%) of these participants had an intrapartum Caesarean delivery. They analysed the importance of clinical parameters including maternal age, maternal height, maternal weight and Bishop score. Ultrasonographic parameters documented included foetal biparietal diameter, abdominal circumference, estimated foetal weight, amniotic fluid index and cervical length. Univariate analysis was used to confirm normal distribution. This was conducted using the Student's t-test and Mann-Whitney U test amongst others. Multiple logistic regression analysis was utilised to identify which parameters were most associated with primary Caesarean delivery.

The five most significant parameters in predicting the risk of Caesarean delivery in nulliparous women were as follows: Maternal age OR 1.19 (95% confidence interval [CI], 1.09–1.30], P < 0.0001; maternal height (cm) OR 0.89 (95% confidence interval [CI], 0.84–0.95), P 0.001; foetal abdominal circumference (cm) OR 1.55 (95% confidence interval [CI], 1.23–1.97), P < 0.0001 and estimated foetal weight (g) OR 1.002 (95% confidence interval [CI], 1.001–1.004), P < 0.000. A prediction model was developed based on these significant parameters. The model was constructed using stepwise forward logistic regression analysis of the potential

predictors identified and the authors concluded that this could be of benefit in assisting decision-making around the most appropriate mode of delivery for women.

This study was designed as a prospective observational study with a sample size of 453 women. However, it should be noted that the authors did not consider examine BMI as a potential predictor. This has been shown by many studies in the literature, some of which have already been mentioned [98, 123] in this literature review as being highly predictive for intrapartum Caesarean delivery. The authors also cautioned that the predictive performance of the model might be overstated as its measures of discrimination are derived from the same analysis that was used to derive the model. They recommended further studies to validate this model in other study populations.

Mazouni et al. also developed and validated a nomogram to predict the risk of Caesarean delivery in macrosomic infants [124]. This was developed using the data collated from 246 women initially and validated in a further study of 206 women in Marseille, France. Interestingly, this study also included multiparous women. The final key predictors, which were incorporated into the nomogram, were: maternal age ($p = 0.01$), maternal height ($p = 0.02$), parity ($p < 0.001$), and previous Caesarean section ($p = 0.009$). This study did not examine any ultrasonographic details and instead it retrospectively examined the maternal data of women who had delivered a baby >4000 g.

Burke et al. published in 2017 a similar conjugate model [125] that represents the predecessor for the subject of this thesis. The genesis study was a prospective observational study, which recruited 2336 low-risk nulliparous women from the island of Ireland from October 2012 to June 2015. These women attended for ultrasound assessment and collection of maternal anthropometric data from 38 + 0 weeks of pregnancy until 40 + 6 weeks of pregnancy and their delivery outcomes were later collated. Genesis found that five parameters were noted to be the most significant predictors of risk of a nulliparous women undergoing intrapartum Caesarean section delivery. These 5 parameters were advancing maternal age OR, 1.21 (95% confidence interval [CI], 1.09–1.34), P = .0005; increasing maternal BMI OR, 1.29 (95% CI, 1.17–1.42), P < 0.0001; shorter maternal height OR, 1.72 (95% CI, 1.54–1.92), P < 0.0001; larger foetal HC OR, 1.27 (95% CI, 1.13–1.42), P = 0.0001; and larger foetal AC OR, 1.23 (95% CI, 1.1–1.37) P = .0004.

These five predictors were then used to develop a nomogram to individually calculate each nulliparous woman's risk for requiring intrapartum Caesarean delivery.

4. Conclusions

We have highlighted the benefits of risk prediction models in many aspects of healthcare. We know from our own reading that these models have been developed in the field of obstetrics and particularly with the interest of predicting intrapartum caesarean delivery.

However, we are still awaiting a validated successful model, which may be used in clinical practice. We have also not identified any research studies examining the usage of Artificial Intelligence to aid with risk prediction or any randomised trials reviewing the merits of elective Caesarean delivery versus trial of labour in the event of cephalo-pelvic disproportion.

A focus group amongst expectant first-time mothers in our unit confirmed that women would be keen on the introduction of a risk predictive tool, which would be individualised for each woman. They felt that this would aid them in their decision-making and birth planning.

We can see from other areas of medicine that risk predictive tools are a valuable asset for clinicians in their optimum care of patients. To date, we have not found a risk predictive tool, which is in routine clinical use specifically for predicting intrapartum caesarean delivery.

Conflict of interest

The authors declare no conflict of interest.

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References

[1] Allen VM, O'Connell CM, Baskett TF. Maternal and perinatal morbidity of caesarean delivery at full cervical dilatation compared with caesarean delivery in the first stage of labour. BJOG: An International Journal of Obstetrics and Gynaecology. 2005;**112**(7):986-990

[2] Suja D, Manjusha V, Simi B, Nazeema. Study of maternal outcome of emergency and elective caesarean section in a semi-rural tertiary hospital. National Journal of Medical Research. 2014;**4**(1)

[3] Magann EF, Evans S, Hutchinson M, Collins R, Lanneau G, Morrison JC. Postpartum hemorrhage after cesarean delivery: An analysis of risk factors. Southern Medical Journal. 2005;**98**(7):681-685

[4] Smaill FM, Grivell RM. Antibiotic prophylaxis versus no prophylaxis for preventing infection after cesarean section. The Cochrane Database of Systematic Reviews. 2014;**10**:Cd007482

[5] Loudon JA, Groom KM, Hinkson L, Harrington D, Paterson-Brown S. Changing trends in operative delivery performed at full dilatation over a 10-year period. Journal of Obstetrics and Gynaecology: The Journal of the Institute of Obstetrics and Gynaecology. 2010;**30**(4):370-375

[6] Pergialiotis V, Vlachos DG, Rodolakis A, Haidopoulos D, Thomakos N, Vlachos GD. First versus second stage C/S maternal and neonatal morbidity: A systematic review and meta-analysis. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2014;**175**:15-24

[7] Yang X-J, Sun S-S. Comparison of maternal and fetal complications in elective and emergency cesarean section: A systematic review and meta-analysis. Archives of Gynecology and Obstetrics. 2017;**296**(3):503-512

[8] Organisation for Economic Co-operation and Development. Caesarean Sections: Health at a Glance 2017: OECD Indicators. OECD Publishing; 2017

[9] The Lancet. Stemming the global caesarean section epidemic. Lancet. 2018;**392**(10155):1279

[10] Martin JA, Hamilton BE, Osterman MJK, Driscoll AK, Drake P. Births: Final data for 2016. National Vital Statistics Reports: From The Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System. 2018;**67**(1):1-55

[11] Betran AP, Torloni MR, Zhang J, Ye J, Mikolajczyk R, Deneux-Tharaux C, et al. What is the optimal rate of caesarean section at population level? A systematic review of ecologic studies. Reproductive Health. 2015;**12**:57

[12] Betran AP, Ye J, Moller AB, Zhang J, Gulmezoglu AM, Torloni MR. The increasing trend in caesarean section rates: Global, regional and national estimates: 1990-2014. PLoS One. 2016;**11**(2):e0148343

[13] Ye J, Betran AP, Guerrero Vela M, Souza JP, Zhang J. Searching for the optimal rate of medically necessary cesarean delivery. Birth. 2014;**41**(3):237-244

[14] Betran AP, Temmerman M, Kingdon C, Mohiddin A, Opiyo N, Torloni MR, et al. Interventions to reduce unnecessary caesarean sections in healthy women and babies. Lancet. 2018;**392**(10155):1358-1368

[15] World Health Organization. WHO Statement on Caesarean Section Rates [WHO/RHR/15.02]. Geneva: World Health Organization; 2015

[16] Mazzoni A, Althabe F, Liu NH, Bonotti AM, Gibbons L, Sanchez AJ, et al. Women's preference for caesarean section: A systematic review and meta-analysis of observational studies. BJOG: An International Journal of Obstetrics and Gynaecology. 2011;**118**(4):391-399

[17] Robson SJ, Tan WS, Adeyemi A, Dear KB. Estimating the rate of cesarean section by maternal request: Anonymous survey of obstetricians in Australia. Birth. 2009;**36**(3):208-212

[18] Murray SF. Relation between private health insurance and high rates of caesarean section in Chile: Qualitative and quantitative study. British Medical Journal. 2000;**321**(7275):1501-1505

[19] Safe prevention of the primary cesarean delivery. Obstetric care consensus No. 1. American College of Obstetricians and Gynecologists. Obstetrics and Gynecology. 2014;**123**:693-711

[20] Gamble JA, Creedy DK. Women's preference for a cesarean section: Incidence and associated factors. Birth. 2001;**28**(2):101-110

[21] Hildingsson I, Rådestad I, Rubertsson C, Waldenström U. Few women wish to be delivered by caesarean section. BJOG: An International Journal of Obstetrics and Gynaecology. 2002;**109**(6):618-623

[22] Osis MJ, Padua KS, Duarte GA, Souza TR, Faundes A. The opinion of Brazilian women regarding vaginal labor and cesarean section. International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics. 2001;**75**(Suppl 1):S59-S66

[23] Potter JE, Berquo E, Perpetuo IH, Leal OF, Hopkins K, Souza MR, et al. Unwanted caesarean sections among public and private patients in Brazil: Prospective study. British Medical Journal. 2001;**323**(7322):1155-1158

[24] Angeja AC, Washington AE, Vargas JE, Gomez R, Rojas I, Caughey AB. Chilean women's preferences regarding mode of delivery: Which do they prefer and why? BJOG: An International Journal of Obstetrics and Gynaecology. 2006;**113**(11):1253-1258

[25] Vogenberg FR. Predictive and prognostic models: Implications for healthcare decision-making in a modern recession. American Health & Drug Benefits. 2009;**2**(6):218-222

[26] Perel P, Edwards P, Wentz R, Roberts I. Systematic review of prognostic models in traumatic brain injury. BMC Medical Informatics and Decision Making. 2006;**6**:38

[27] Abu-Hanna A, Lucas PJ. Prognostic models in medicine. AI and statistical approaches. Methods of Information in Medicine. 2001;**40**(1):1-5

[28] Justice AC, Covinsky KE, Berlin JA. Assessing the generalizability of prognostic information. Annals of Internal Medicine. 1999;**130**(6):515-524

[29] Lloyd-Jones DM, Larson MG, Beiser A, Levy D. Lifetime risk of developing coronary heart disease. Lancet. 1999;**353**(9147):89-92

[30] Carlson B. Predictive modeling, sharp lens on near future. Managed Care. 2003;**12**(7):16-21

[31] Kleinrouweler CE, Cheong-See FM, Collins GS, Kwee A, Thangaratinam S, Khan KS, et al. Prognostic models in obstetrics: Available, but far from applicable. American Journal of Obstetrics and Gynecology. 2016;**214**(1):79-90.e36

[32] Apgar V. A proposal for a new method of evaluation of the newborn infant. Current Researches in Anesthesia & Analgesia. 1953;**32**(4):260-267

[33] Bishop EH. Pelvic scoring for elective induction. Obstetrics and Gynecology. 1964;**24**:266-268

[34] Casey BM, McIntire DD, Leveno KJ. The continuing value of the Apgar score for the assessment of newborn infants. The New England Journal of Medicine. 2001;**344**(7):467-471

[35] Finster M, Wood M. The Apgar score has survived the test of time. Anesthesiology. 2005;**102**(4):855-857

[36] James BC. Making it easy to do it right. The New England Journal of Medicine. 2001;**345**(13):991-993

[37] Reilly BM, Evans AT. Translating clinical research into clinical practice: Impact of using prediction rules to make decisions. Annals of Internal Medicine. 2006;**144**(3):201-209

[38] Cheong-See F, Allotey J, Marlin N, Mol BW, Schuit E, Ter Riet G, et al. Prediction models in obstetrics: Understanding the treatment paradox and potential solutions to the threat it poses. BJOG: An International Journal of Obstetrics and Gynaecology. 2016;**123**(7):1060-1064

[39] Rao SC, Chhatriwalla AK, Kennedy KF, Decker CJ, Gialde E, Spertus JA, et al. Pre-procedural estimate of individualized bleeding risk impacts physicians' utilization of bivalirudin during percutaneous coronary intervention. Journal of the American College of Cardiology. 2013;**61**(18):1847-1852

[40] Schuit E, Groenwold RH, Harrell FE Jr, de Kort WL, Kwee A, Mol BW, et al. Unexpected predictor-outcome associations in clinical prediction research: Causes and solutions. Canadian Medical Association Journal. 2013;**185**(10):E499-E505

[41] Thangaratinam S, Allotey J, Marlin N, Dodds J, Cheong-See F, von Dadelszen P, et al. Prediction of complications in early-onset pre-eclampsia [PREP]: Development and external multinational validation of prognostic models. BMC Medicine. 2017;**15**(1):68

[42] Timmerman D, Van Calster B, Testa A, Savelli L, Fischerova D, Froyman W, et al. Predicting the risk of malignancy in adnexal masses based on the simple rules from the international ovarian tumor analysis group. American Journal of Obstetrics and Gynecology. 2016;**214**(4):424-437

[43] Timmerman D, Testa AC, Bourne T, Ameye L, Jurkovic D, Van Holsbeke C, et al. Simple ultrasound-based rules for the diagnosis of ovarian cancer. Ultrasound in Obstetrics & Gynecology. 2008;**31**(6):681-690

[44] Kansagara D, Englander H, Salanitro A, Kagen D, Theobald C, Freeman M, et al. Risk prediction models for hospital readmission: A systematic review. Journal of the American Medical Association. 2011;**306**(15):1688-1698

[45] Jack BW, Chetty VK, Anthony D, Greenwald JL, Sanchez GM, Johnson AE, et al. A reengineered hospital discharge program to decrease rehospitalization: A randomized trial. Annals of Internal Medicine. 2009;**150**(3):178-187

[46] Krumholz HM, Brindis RG, Brush JE, Cohen DJ, Epstein AJ, Furie K, et al. Standards for statistical models used for public reporting of health outcomes: An American Heart Association scientific statement from the quality of care and outcomes research interdisciplinary writing group: Cosponsored by the council on epidemiology and prevention and the stroke council. Endorsed by the American College of Cardiology Foundation. Circulation. 2006;**113**(3):456-462

[47] Toll DB, Janssen KJ, Vergouwe Y, Moons KG. Validation, updating and impact of clinical prediction rules: A review. Journal of Clinical Epidemiology. 2008;**61**(11):1085-1094

[48] Moons KG, Kengne AP, Woodward M, Royston P, Vergouwe Y, Altman DG, et al. Risk prediction models: I. Development, internal validation, and assessing the incremental value of a new [bio]marker. Heart. 2012;**98**(9):683-690

[49] Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;**97**(18):1837-1847

[50] Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: The SCORE project. European Heart Journal. 2003;**24**(11):987-1003

[51] Woodward M, Brindle P, Tunstall-Pedoe H. Adding social deprivation and family history to cardiovascular risk assessment: The ASSIGN score from the Scottish heart health extended cohort [SHHEC]. Heart. 2007;**93**(2):172-176

[52] Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation [EuroSCORE]. European Journal of Cardio-Thoracic Surgery: Official Journal of The European Association for Cardio-Thoracic Surgery. 1999;**16**(1):9-13

[53] Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Münster [PROCAM] study. Circulation. 2002;**105**(3):310-315

[54] Wells PS, Anderson DR, Bormanis J, Guy F, Mitchell M, Gray L, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. Lancet. 1997;**350**(9094):1795-1798

[55] Lloyd-Jones DM. Cardiovascular risk prediction: Basic concepts, current status, and future directions. Circulation. 2010;**121**(15):1768-1777

[56] Moons KG. Criteria for scientific evaluation of novel markers: A perspective. Clinical Chemistry. 2010;**56**(4):537-541

[57] Steinkamp HJ, Zwicker C, Langer M, Mathe M, Ehritt C, Neumann K, et al. Reactive enlargement of cervical lymph nodes and cervical lymph node metastases: Sonography [M/Q quotient] and computed tomography. Aktuelle Radiologie. 1992;**2**(4):188-195

[58] Cardoso F, Harbeck N, Fallowfield L, Kyriakides S, Senkus E. Locally recurrent or metastatic breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Annals of Oncology: Official Journal of the European Society for Medical Oncology. 2012;**23**(Suppl 7):vii11-vii19

[59] Oostendorp LJ, Stalmeier PF, Donders AR, van der Graaf WT, Ottevanger PB. Efficacy and safety of palliative chemotherapy for patients with advanced breast cancer pretreated with anthracyclines and taxanes: A systematic review. The Lancet Oncology. 2011;**12**(11):1053-1061

[60] Alfarouk KO, Stock CM, Taylor S, Walsh M, Muddathir AK, Verduzco D, et al. Resistance to cancer chemotherapy: Failure in drug response from ADME to P-gp. Cancer Cell International. 2015;**15**:71

[61] Mucaki EJ, Zhao JZL, Lizotte DJ, Rogan PK. Predicting responses to platin chemotherapy agents with biochemically-inspired machine learning. Signal Transduction and Targeted Therapy. 2019;**4**(1):1

[62] Akamatsu N, Nakajima H, Ono M, Miura Y. Increase in acetyl CoA synthetase activity after phenobarbital treatment. Biochemical Pharmacology. 1975;**24**(18):1725-1727

[63] Burrell RA, McGranahan N, Bartek J, Swanton C. The causes and consequences of genetic heterogeneity in cancer evolution. Nature. 2013;**501**(7467):338-345

[64] Block KI, Gyllenhaal C, Lowe L, Amedei A, Amin ARMR, Amin A, et al. Designing a broad-spectrum integrative approach for cancer prevention and treatment. Seminars in Cancer Biology. 2015;**35**(Suppl):S276-s304

[65] Ubels J, Sonneveld P, van Beers EH, Broijl A, van Vliet MH, de Ridder J. Predicting treatment benefit in multiple myeloma through simulation of alternative treatment effects. Nature Communications. 2018;**9**([1]):2943

[66] Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, et al. SEER Cancer Statistics Review 1975-2015. Bethesda, MD: National Cancer Institute; 2018. Available from: https://seer.cancer.gov/csr/1975_2015/

[67] Lohr JG, Stojanov P, Carter SL, Cruz-Gordillo P, Lawrence MS, Auclair D, et al. Widespread genetic heterogeneity in multiple myeloma: Implications for targeted therapy. Cancer Cell. 2014;**25**(1):91-101

[68] Boyle A, Reddy UM, Landy HJ, Huang C-C, Driggers RW, Laughon SK. Primary cesarean delivery in the United States. Obstetrics and Gynecology. 2013;**122**(1):33-40

[69] Mocanu EV, Greene RA, Byrne BM, Turner MJ. Obstetric and neonatal outcome of babies weighing more than 4.5 kg: An analysis by parity. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2000;**92**(2):229-233

[70] Shechter Y, Levy A, Wiznitzer A, Zlotnik A, Sheiner E. Obstetric complications in grand and great grand multiparous women. The Journal of Maternal-Fetal & Neonatal Medicine: The Official Journal of The European Association of Perinatal Medicine, The Federation of Asia and Oceania Perinatal Societies, The International Society of Perinatal Obstetricians. 2010;**23**(10):1211-1217

[71] Zhu BP, Grigorescu V, Le T, Lin M, Copeland G, Barone M, et al. Labor dystocia and its association with interpregnancy interval. American Journal of Obstetrics and Gynecology. 2006;**195**(1):121-128

[72] Algovik M, Kivinen K, Peterson H, Westgren M, Kere J. Genetic evidence of multiple loci in dystocia-difficult labour. BMC Medical Genetics. 2010;**11**(1):105

[73] Galvin DM, Burke N, Burke G, Breathnach F, McAuliffe F, Morrison J, et al. 94: Accuracy of prenatal detection of macrosomia >4,000g and outcomes in the absence of intervention: Results of the prospective multicenter genesis study. American Journal of Obstetrics and Gynecology. 2017;**216**(1):S68

[74] Chauhan SP, Grobman WA, Gherman RA, Chauhan VB, Chang G, Magann EF, et al. Suspicion and treatment of the macrosomic fetus: A review. American Journal of Obstetrics and Gynecology. 2005;**193**(2):332-346

[75] Kennelly MM, Anjum R, Lyons S, Burke G. Postpartum fetal head circumference and its influence on labour duration in nullipara. Journal of Obstetrics and Gynaecology: The Journal of The Institute of Obstetrics and Gynaecology. 2003;**23**(5):496-499

[76] Elvander C, Hogberg U, Ekeus C. The influence of fetal head circumference on labor outcome: A population-based register study.

Acta Obstetricia et Gynecologica Scandinavica. 2012;**91**(4):470-475

[77] Valsky DV, Lipschuetz M, Bord A, Eldar I, Messing B, Hochner-Celnikier D, et al. Fetal head circumference and length of second stage of labor are risk factors for levator ani muscle injury, diagnosed by 3-dimensional transperineal ultrasound in primiparous women. American Journal of Obstetrics and Gynecology. 2009;**201**(1):91.e1-91.e7

[78] Caldwell WE, Moloy HC, Anthony D'esopo D. A roentgenologic study of the mechanism of engagement of the fetal head. American Journal of Obstetrics and Gynecology. 1934;**28**(6):824-841

[79] Gardberg M, Laakkonen E, Salevaara M. Intrapartum sonography and persistent occiput posterior position: A study of 408 deliveries. Obstetrics and Gynecology. 1998;**91** (5 Pt 1):746-749

[80] Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Gilstrap III LC, Wenstrom KD. Williams Obstetrics. 22nd ed. New York: McGraw Hill; 2005

[81] Baskett TF, Calder AA, Arulkumaran S, Munro Kerr's Pr M. Operative Obstetrics. 10th ed. London: Baillie're Tindall; 1982

[82] Akmal S, Kametas N, Tsoi E, Howard R, Nicolaides KH. Ultrasonographic occiput position in early labour in the prediction of caesarean section. BJOG: An International Journal of Obstetrics and Gynaecology. 2004;**111**(6):532-536

[83] Fitzpatrick M, McQuillan K, O'Herlihy C. Influence of persistent occiput posterior position on delivery outcome. Obstetrics and Gynecology. 2001;**98**(6):1027-1031

[84] Ponkey SE, Cohen AP, Heffner LJ, Lieberman E. Persistent fetal occiput posterior position: Obstetric outcomes. Obstetrics and Gynecology. 2003;**101** (5 Pt 1):915-920

[85] Sizer AR, Nirmal DM. Occipitoposterior position: Associated factors and obstetric outcome in nulliparas. Obstetrics and Gynecology. 2000;**96**(5 Pt 1):749-752

[86] Ulset E, Undheim R, Malterud K. Has the obesity epidemic reached Norway? Tidsskrift for den Norske Lægeforening: Tidsskrift for Praktisk Medicin, ny Række. 2007;**127**(1):34-37

[87] Ludford I, Scheil W, Tucker G, Grivell R. Pregnancy outcomes for nulliparous women of advanced maternal age in South Australia, 1998-2008. The Australian and New Zealand Journal of Obstetrics and Gynaecology. 2012;**52**(3):235-241

[88] Timofeev J, Reddy UM, Huang CC, Driggers RW, Landy HJ, Laughon SK. Obstetric complications, neonatal morbidity, and indications for cesarean delivery by maternal age. Obstetrics and Gynecology. 2013;**122**(6):1184-1195

[89] Luke B, Brown MB. Elevated risks of pregnancy complications and adverse outcomes with increasing maternal age. Human Reproduction. 2007;**22**(5):1264-1272

[90] Bayrampour H, Heaman M. Advanced maternal age and the risk of cesarean birth: A systematic review. Birth. 2010;**37**(3):219-226

[91] Bell JS, Campbell DM, Graham WJ, Penney GC, Ryan M, Hall MH. Can obstetric complications explain the high levels of obstetric interventions and maternity service use among older womsen? A retrospective analysis of routinely collected data. BJOG: An International Journal of Obstetrics and Gynaecology. 2001;**108**(9):910-918

[92] Herstad L, Klungsoyr K, Skjaerven R, Tanbo T, Forsen L, Abyholm T, et al. Maternal age and emergency operative deliveries at term: A population-based registry study among low-risk primiparous women. BJOG: An International Journal of Obstetrics and Gynaecology. 2015;**122**(12):1642-1651

[93] Klemetti R, Gissler M, Sainio S, Hemminki E. Associations of maternal age with maternity care use and birth outcomes in primiparous women: A comparison of results in 1991 and 2008 in Finland. BJOG: An International Journal of Obstetrics and Gynaecology. 2014;**121**(3):356-362

[94] Waldenstrom U, Gottvall K, Rasmussen S. Caesarean section in nulliparous women of advanced maternal age has been reduced in Sweden and Norway since the 1970s: A register-based study. BJOG: An International Journal of Obstetrics and Gynaecology. 2012;**119**(13):1591-1596

[95] Herstad L, Klungsoyr K, Skjaerven R, Tanbo T, Eidem I, Forsen L, et al. Maternal age and elective cesarean section in a low-risk population. Acta Obstetricia et Gynecologica Scandinavica. 2012;**91**(7):816-823

[96] Herstad L, Klungsøyr K, Skjærven R, Tanbo T, Forsén L, Åbyholm T, et al. Elective cesarean section or not? Maternal age and risk of adverse outcomes at term: A population-based registry study of low-risk primiparous women. BMC Pregnancy and Childbirth. 2016;**16**:230

[97] Peipert JF, Bracken MB. Maternal age: An independent risk factor for cesarean delivery. Obstetrics and Gynecology. 1993;**81**(2):200-205

[98] Young TK, Woodmansee B. Factors that are associated with cesarean delivery in a large private practice: The importance of prepregnancy body mass index and weight gain. American Journal of Obstetrics and Gynecology. 2002;**187**(2):32-38. Discussion 8-20

[99] Mittal P, Romero R, Tarca AL, Draghici S, Nhan-Chang C-L, Chaiworapongsa T, et al. A molecular signature of an arrest of descent in human parturition. American Journal of Obstetrics and Gynecology. 2011;**204**(2):177.e15-177.e33

[100] Johnson M, Stewart H, Langdon R, Kelly P, Yong L. Women-centred care and caseload models of midwifery. Collegian. 2003;**10**(1):30-34

[101] Homer CS, Davis GK, Brodie PM, Sheehan A, Barclay LM, Wills J, et al. Collaboration in maternity care: A randomised controlled trial comparing community-based continuity of care with standard hospital care. BJOG: An International Journal of Obstetrics and Gynaecology. 2001;**108**(1):16-22

[102] Harvey S, Jarrell J, Brant R, Stainton C, Rach D. A randomized, controlled trial of nurse-midwifery care. Birth. 1996;**23**(3):128-135

[103] Waldenstrom U, Turnbull D. A systematic review comparing continuity of midwifery care with standard maternity services. British Journal of Obstetrics and Gynaecology. 1998;**105**(11):1160-1170

[104] Brocklehurst P, Hardy P, Hollowell J, Linsell L, Macfarlane A, McCourt C, et al. Perinatal and maternal outcomes by planned place of birth for healthy women with low risk pregnancies: The birthplace in England national prospective cohort study. British Medical Journal. 2011;**343**:d7400

[105] AbouZahr CWT, Stanton C, Hill K. Maternal Mortality. World Health Stat Q 199. Vol. 49. 1995. pp. 77-87

[106] Kwast BE. Obstructed labour: Its contribution to maternal mortality. Midwifery. 1992;**8**(1):3-7

[107] Nkata M. Maternal mortality due to obstructed labor. International Journal of Gynecology & Obstetrics. 1997;**57**(1):65-66

[108] Smith JB, Burton NF, Nelson G, Fortney JA, Duale S. Hospital deaths in a high risk obstetric population: Karawa, Zaire. International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics. 1986;**24**(3):225-234

[109] Maharaj D. Assessing cephalopelvic disproportion: Back to the basics. Obstetrical & Gynecological Survey. 2010;**65**(6):387-395

[110] Liselele HB, Boulvain M, Tshibangu KC, Meuris S. Maternal height and external pelvimetry to predict cephalopelvic disproportion in nulliparous African women: A cohort study. BJOG: An International Journal of Obstetrics and Gynaecology. 2000;**107**(8):947-952

[111] Chalmers I, Enkin MKM, editors. Suspected Fetopelvic Disproportion. Oxford: Oxford University Press; 1989

[112] Rozenholc AT, Ako SN, Leke RJ, Boulvain M. The diagnostic accuracy of external pelvimetry and maternal height to predict dystocia in nulliparous women: A study in Cameroon. BJOG: An International Journal of Obstetrics and Gynaecology. 2007;**114**(5):630-635

[113] Morgan MA, Thurnau GR. Efficacy of the fetal-pelvic index in nulliparous women at high risk for fetal-pelvic disproportion. American Journal of Obstetrics and Gynecology. 1992;**166**(3):810-814

[114] Pattinson RC, Cuthbert A, Vannevel V. Pelvimetry for fetal cephalic presentations at or near term for deciding on mode of delivery. The Cochrane Database of Systematic Reviews. 2017;**3**:Cd000161

[115] Abitbol MM, Taylor UB, Castillo I, Rochelson BL. The cephalopelvic disproportion index. Combined fetal sonography and x-ray pelvimetry for early detection of cephalopelvic disproportion. The Journal of Reproductive Medicine. 1991;**36**(5):369-373

[116] Sporri S, Thoeny HC, Raio L, Lachat R, Vock P, Schneider H. MR imaging pelvimetry: A useful adjunct in the treatment of women at risk for dystocia? American Journal of Roentgenology. 2002;**179**(1):137-144

[117] Zaretsky MV, Alexander JM, McIntire DD, Hatab MR, Twickler DM, Leveno KJ. Magnetic resonance imaging pelvimetry and the prediction of labor dystocia. Obstetrics and Gynecology. 2005;**106**(5 Pt 1):919-926

[118] Grobman WA, Lai Y, Landon MB, Spong CY, Leveno KJ, Rouse DJ, et al. Development of a nomogram for prediction of vaginal birth after cesarean delivery. Obstetrics and Gynecology. 2007;**109**(4):806-812

[119] Chaillet N, Bujold E, Dube E, Grobman WA. Validation of a prediction model for vaginal birth after caesarean. Journal of Obstetrics and Gynaecology Canada. 2013;**35**(2):119-124

[120] Costantine MM, Fox K, Byers BD, Mateus J, Ghulmiyyah LM, Blackwell S, et al. Validation of the prediction model for success of vaginal birth after cesarean delivery. Obstetrics and Gynecology. 2009;**114**(5):1029-1033

[121] Maykin MM, Mularz AJ, Lee LK, Valderramos SG. Validation of a prediction model for vaginal birth after Cesarean delivery reveals unexpected success in a diverse American population. AJP Reports. 2017;**7**(1):e31-ee8

[122] Kim SN, Park KH, Jung HJ, Hong JS, Shin DM, Kang WS. Clinical

and sonographic parameters at 37 weeks' gestation for predicting the risk of primary Cesarean delivery in nulliparous women. Ultrasound in Obstetrics & Gynecology. 2010;**36**(4):486-492

[123] Roman H, Goffinet F, Hulsey TF, Newman R, Robillard PY, Hulsey TC. Maternal body mass index at delivery and risk of caesarean due to dystocia in low risk pregnancies. Acta Obstetricia et Gynecologica Scandinavica. 2008;**87**(2):163-170

[124] Mazouni C, Rouzier R, Collette E, Menard JP, Magnin G, Gamerre M, et al. Development and validation of a nomogram to predict the risk of cesarean delivery in macrosomia. Acta Obstetricia et Gynecologica Scandinavica. 2008;**87**(5):518-523

[125] Burke N, Burke G, Breathnach F, McAuliffe F, Morrison JJ, Turner M, et al. Prediction of cesarean delivery in the term nulliparous woman: Results from the prospective, multicenter genesis study. American Journal of Obstetrics and Gynecology. 2017;**216**(6):598.e1-598.e11