


STUDY PROTOCOL

Developing and validating the Caesarean risk assessment nomogram and comparing the effect of cervical ripening balloon, evening primrose oil and misoprostol on childbirth outcomes in term pregnancies: A study protocol

Shahla Hemmatzadeh¹ | Fatemeh Abbasalizadeh² | Sakineh Mohammad-Alizadeh-Charandabi³ | Mohammad Asghari Jafarabady⁴ | Mojgan Mirghafourvand⁵ 

¹Students' Research Committee, Midwifery Department, Tabriz University of Medical sciences, Tabriz, Iran

²Department of Gynecology, Faculty of medicine, Tabriz University of Medical Sciences, Tabriz, Iran

³Department of Midwifery, Faculty of Nursing and Midwifery, Tabriz University of Medical Sciences, Tabriz, Iran

⁴Mohammad Asghari, Faculty of health, Department of Epidemiology, Tabriz University of Medical Sciences, Tabriz, Iran

⁵Social Determinants of Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

Correspondence

Mojgan Mirghafourvand, Social determinants of Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
Email: mirghafourvand@gmail.com

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Abstract

Aim: To develop and validate the nomogram for risk estimation of Caesarean delivery and to compare the effect of cervical ripening balloon, evening primrose oil (EPO) and misoprostol on Bishop Score and duration of the first stage of labour.

Design: The first phase is a prospective study, and the second phase is a randomized controlled trial.

Methods: In the first phase, the nomogram will be developed and validated over 300 participants, and in the second phase, the 90 participants will be allocated to three groups: vaginal 25mcg misoprostol, vaginal 4000mg EPO and double-balloon catheter, through block randomization method. The Bishop score will be evaluated every 4 hr, and if required the same dose will be repeated. Maximum waiting time for balloon is 12 hr if not effective, the catheter will be removed, and other interventions will be done according to guidelines.

Discussion: The nomogram will help informed decision-making for women undergoing an induction with an unfavourable cervix and introducing effective low-complication methods of labour induction can improve the pregnancy outcomes.

KEYWORDS

Bishop score, cook cervical ripening balloon, evening primrose oil, labour Induction, misoprostol, unfavourable cervix

1 | INTRODUCTION

Labour is a physiologic phenomenon which begins spontaneously at the gestational age of 38–42 weeks. However, about 4%–9% of

pregnancies last more than this time; this condition is called post-term pregnancy (Bleicher et al., 2017; Hall et al., 2012). According to the American College of Obstetricians and Gynecologists (ACOG), post-term pregnancy refers to pregnancies progressing beyond

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42^{0/7} weeks of gestation, that is, ≥ 294 days from the first day of the last menstrual period (American College of Obstetricians & Gynecologists, 2014). Post-term pregnancy can increase the rate of prenatal morbidity and mortality (Maoz et al., 2019).

Many clinical trials and meta-analyses support the idea that in comparison with expectant management, labour induction after 41 weeks is associated with a significant reduction in perinatal mortality, meconium aspiration and Caesarean delivery (Khan et al., 2006; Maoz et al., 2019; Mozurkewich et al., 2009). A successful induction depends on several factors, in particular the Bishop score which assesses the dilatation, effacement, consistency and position of the cervix and the station of foetal presenting part (Khooshideh et al., 2017; Vitner et al., 2020). A high Bishop score (≥ 6) is correlated with a successful labour induction and vaginal delivery, and a low Bishop score (< 6) is correlated with high rates of failed induction and Caesarean delivery (Navve et al., 2017).

Unfortunately, in many induction cases, the Bishop score is low, requiring ripening techniques (Güngördük et al., 2012; Maoz et al., 2019). About 22% of pregnancies undergo labour induction of which almost one-third eventually lead to C-section (Jakub et al., 2020). There are a limited number of studies regarding the prediction of delivery outcomes of women with an unfavourable cervix who need induction. The known associated risks of prolonged labour and failed induction clinically necessitate an accurate prediction of the Caesarean section likelihood. In addition, after careful detection and exclusion of specific risks, it seems appropriate to let women make an informed decision about the type of management they prefer (Coates et al., 2019; Levine et al., 2018). Jochum et al. in the United States recently validated a nomogram and labour induction calculator for the first time on more than 200,000 pregnant women undergoing labour induction. A nomogram is a graphic calculating device, a two-dimensional diagram designed to allow the approximate graphic computation of the likelihood of a clinical event (Bianco, 2006). It was also used to create a user-friendly web-based calculator that gives the percentage likelihood of Caesarean delivery (<http://www.uphs.upenn.edu/obgyn/labor-induction-calculator/>). This calculator can be used to increase the awareness of induction-undergoing women with an unfavourable cervix. The Bishop score is neither a good predictor of labour induction success, nor a predictor of maternal or neonatal adverse outcomes and complications. Unfortunately, this instrument is not available and used in Iran for the management of post-term pregnancy; therefore, this research aims to use it for the first time in Iran and validate the Caesarean delivery risk estimation nomogram.

Labour can be induced using misoprostol, dinoprostone and oxytocin as well as Foley catheter, alternative medicine, acupuncture and herbals (Dashe et al., 2018). Evening primrose oil (EPO) is useful herbal oil for labour induction (Mahboubi, 2019). Its most important constituents include linoleic acid (60%–65%) and gamma-linolenic acid (7%–14%) which are natural precursors of prostaglandins. Gamma-linolenic acid is an unsaturated fatty acid which can directly convert to prostaglandins including PGE₁. Limited studies have concluded that this product can induce labour through cervical ripening (Simon et al., 2014). Many midwives propose pregnant women to

consume 500–1000 mg/day EPO from the 34th week and increase the dose up to 2000 mg/day from the beginning of the 38th week. Due to inadequate clinical evidence on EPO for labour induction, further research should be done (Hall et al., 2012; Ty-Torredes, 2006).

Cervical ripening balloon (CRB) is one of the few mechanical induction methods approved by the Food and Drug Administration (FDA). In comparison with oxytocin and prostaglandins, it can cause greater cervical dilatation, reduce the Caesarean delivery rate, shorten the induction initiation and delivery interval, and increase the chance of success without considerable side effects (Ebeid & Nassif, 2013). Unlike the Foley catheter, the cervical ripening balloon is made of (allergy-free) silicon and two balloons. It causes gradual and constant pressure from both sides on the cervix and increases the secretion of prostaglandins. This method is not widely used in Iran. Considering its great effect and easy tolerance by mothers, it can be used in labour induction (Vitner et al., 2020).

Misoprostol or prostaglandin E₁, which is commonly used for labour induction, is approved by the International Federation of Gynecology and Obstetrics (FIGO). This medication is cost-effective and can be accessed in more than 80 countries throughout the world especially in low-income countries. The usual recommended dose for induction of term pregnancy is 25 µg every 3–6 hr applied in the posterior fornix. Misoprostol reduces the rate of Caesarean deliveries and the need for oxytocin. The important considerations when using misoprostol for labour induction include increased incidence of uterine tachysystole with or without impaired foetal heart rate and the possibility of uterine scar rupture in women with previous history of Caesarean section (Tang et al., 2013).

According to the results of a systematic review and meta-analysis, there are a limited number of studies into herbs and non-pharmacological methods and studies comparing the three mentioned interventions, necessitating high-quality studies with larger sample sizes (Ghasemi et al., 2018). In the second phase, the three mentioned methods will be compared.

2 | OUTCOME MEASURES

2.1 | Phase 1

To develop and validate the Caesarean delivery risk estimation nomogram following labour induction in women with unripe cervix.

2.2 | Phase 2

2.2.1 | Primary objectives

1. To compare the mean Bishop score 4, 8, and 12 hr following beginning the intervention in the study groups while controlling the Bishop score before the intervention.
2. To compare the mean duration of the first stage of labour in the study groups.

2.3 | Secondary objectives

1. To compare the mean duration of the second stage of labour in the study groups.
2. To compare the mean duration of the third stage of labour in the study groups.
3. To compare the frequency of Caesarean delivery between the study groups.
4. To compare the first- and fifth-minute neonatal Apgar scores between the study groups.
5. To compare the frequency of administering oxytocin between the study groups.
6. To compare the mean score of satisfaction with delivery between the study groups.
7. To determine the side effects in the study groups.

3 | METHODS

This protocol has been approved by the Ethics Committee of the Tabriz University of Medical Sciences, Tabriz, Iran (code number: IR.TBZMED.REC.1399.141). The study will be implemented in two phases:

3.1 | First phase

This phase is a descriptive-analytical prospective study on 300 term pregnancies with main objective to develop the nomogram of Caesarean delivery risk estimation following labour induction in women with unripe cervix.

3.1.1 | Inclusion criteria

The inclusion criteria include pregnancy of 38 weeks and longer, singleton pregnancy, vertex presentation, indication for labour induction and Bishop score ≤ 6 and dilation ≤ 2 cm.

3.1.2 | Exclusion criteria

The exclusion criteria include maternal mental disorder, multiple foetuses, previous scarring on the uterus, contraindication to misoprostol or a vaginal delivery.

3.1.3 | Sample size

Using the method proposed by Riley et al., (2019), based on up 5 candidate predictor parameters with an anticipated adjusted Nagelkerke's R^2 of at least 0.2, to target an expected shrinkage of 0.90, we need a minimum sample size of 200. We consider 300 cases, 200 for developing the nomogram and 100 cases for external validation.

3.1.4 | Sampling

The researcher will attend the labour and delivery ward of Alzahra, Taleghani and 29 Bahman hospitals in Tabriz city, Iran. The convenience sampling method will be used for sampling. For the women meeting the inclusion criteria, the research goals and methods will be explained. If they were willing to participate, they would sign an informed consent form. Further, 200 participant will be considered for nomogram development using a checklist including the maternal height, BMI in admission, parity, gestational age and modified Bishop Score; then, 100 will be considered for external validation of developed nomogram. The participants will be followed up until the time of delivery, and type of delivery will also be recorded in the relevant checklist.

3.1.5 | Data analysis

After data collection, for developing the nomogram, STATA16 software, along with logistic regression test plus nomolog code, will be used. In addition, using an online calculator at the following website (<http://www.uphs.upenn.edu/labor-induction-calculator/>), the probability of incidence of Caesarean can also be calculated.

3.2 | Second phase

This phase is a double-blind randomized controlled trial, in which the effect of cervical ripening balloon, vaginal 4,000 mg EPO and 25 mcg vaginal misoprostol will be compared regarding the Bishop score and duration of the first stage of labour. Table 1 shows the flow diagram of the study design.

3.2.1 | Primary outcomes

1. Bishop score is equal in the 4,000 mg evening primrose oil group with the misoprostol group after 4, 8 and 12 hr postintervention.
2. Bishop score is equal in the double-balloon group and the misoprostol group after 4, 8 and 12 postintervention.
3. The duration of the first stage of labour is the same in the 4,000 mg EPO group with the misoprostol group.
4. The duration of the first stage of labour is equal in double-balloon and misoprostol groups.

3.2.2 | Secondary outcomes

1. The duration of the second stage of labour is equal between all groups.
2. The duration of the third stage of labour is equal between all groups.

3. The frequency of Caesarean delivery is the same between all groups.
4. The neonatal first- and fifth-minutes Apgar scores are equal between all groups.
5. The frequency of oxytocin use is the same between all groups.
6. Birth satisfaction is the same between all groups.
7. The incidence of side effects is the same between all groups.

3.2.3 | Inclusion criteria

The inclusion criteria include gestational age ≥ 40 weeks, vertex presentation, parity ≤ 4 , singleton pregnancy according to sonography, no contraindication for vaginal delivery, having low-risk pregnancy (there are no active complications and that there are no maternal or foetal factors that place the pregnancy at increased risk for complications), Bishop score ≤ 4 , reactive non-stress test (if baby's heartbeat accelerates to a certain level above the baseline twice or more for at least 15 s each within a 20-min window) at the time of admission, absence of spontaneous uterine contractions (less than three contractions per 30 min) and intact amniotic sac.

3.2.4 | Exclusion criteria

Exclusion criteria include disorders of the amniotic fluid volume, developmental disorders of the foetus, macrosomia, contraindication for consuming evening primrose oil such as history of convulsions in the mother or consuming anticonvulsant drugs, contraindication for labour induction, high-risk pregnancy, and presence of any chronic or systemic disease such as diabetes and hypertension, and existence of scar on the uterus.

3.2.5 | Sample size

The sample size was calculated using G-Power software. Calculated necessary sample size for the primary outcome of the duration of labour was higher than for the other primary outcome. Based on the results of Kalati et al., (2018) with regard to the duration of labour and considering $m_1 = 371.43$, $m_2 = 530.62$, $sd_1 = sd_2 = 223.37$, $\alpha = 0.05$, and Power = 80%, it was then calculated 26 for each group, and effect size was estimated 30.0 according to the formula of $[m_1 (\text{mean duration of labour in experimental group}) - m_2 (\text{mean duration of labour in control group}) / m_2] \times 100$. Finally, considering the possibility of sample size attrition, 30 participants will be chosen for each group. Considering results of Najafi et al., (2019) with regard to Bishop score and considering $m_1 = 7.13$, $m_2 = 5.02$, $sd_1 = 2.09$, $sd_2 = 2.39$, $\alpha = 0.05$, and Power = 95%, the 26 sample size could identify effect size of at least 42.0 on this outcome.

3.2.6 | Sampling

Sample selection will be carried out in the labour and delivery ward of Taleghani, Alzahra and 29 Bahman hospitals in Tabriz city. The eligible women will be selected using the convenience sampling method. All women admitted to labour and delivery ward will be assessed in terms of eligibility criteria. The eligible participants will be provided explanations about the objectives and procedures. In the case of willingness to participate in the study, they will sign written informed consent form. The participants will be sufficiently assured about the confidentiality of information and anonymity when reporting the results. It will also be explained that they are free to quit the study at any stage of intervention with no fear of the possible consequences. Indeed, when they stop their cooperation, no change will occur in provision of routine services to them. The demographic and obstetrics questionnaires and Bishop Checklist will be completed for the participants.

3.2.7 | Randomization

The participants will be randomly assigned to three groups through the stratified block randomization design (stratification based on 1: the number of deliveries; first delivery in one stratum and 2-4 deliveries in other strata and 2: gestational age; 40-41 weeks in one block and 41-42 in another one) using 3 and 6 blocks and an assignment ratio of 1:1:1 in Random Allocation Software. Group 1: a 25 mcg vaginal misoprostol, Group 2: 4 vaginal EPO capsules (each 1,000 mg) and Group 3: CRB catheter. For allocation concealment, the type of intervention will be written on a paper and placed in consecutively numbered opaque envelopes.

3.2.8 | Intervention of the study

EPO 1,000 mg capsule and its placebo will be prepared by Barij Essence Pharmaceutical Company (Tehran, Iran). Also, misoprostol tablet and its placebo will be procured by Samisaz Pharmaceutical Company (Mashhad, Iran). The vital signs of the participants will be recorded before intervention, and NST will also be taken.

The CRB catheterization process: After speculum placement and cervical cleansing, the catheter will be inserted, such that both balloons would enter the internal os of cervix. The internal balloon will be filled with 40 ml sterilized normal saline or distilled water. Then, the device will be withdrawn until it hits the internal os of cervix. Next, the external balloon in the vagina will be filled with 20 ml of the same fluid. When both balloons are fixed, the fluid inside each can be filled to as much as 80 ml. In cases that cervical ripening does not occur up to 12 hr, the catheter would be removed and other interventions will be performed.

The study will be performed as double-blind controlled trial. Both participants and the researcher who will do the intervention

will be blind for two interventions (vaginal misoprostol and vaginal EPO), because of nature of cervical ripening balloon blinding is not possible for it. EPO capsules will be inserted in the posterior fornix, after punching with sterile needle. The Bishop score will be evaluated every 4 hr through vaginal examination, and if required the same dose will be repeated 4 hr later once again. Misoprostol 100 mcg tablet will be divided into four equal parts (each 25 mcg), and if required it will be repeated up to two doses, and as with the EPO capsule, it will be inserted in the posterior fornix.

The examined variables including pre-intervention Bishop score, Bishop score after 4, 8 and 12 hr after intervention, duration of labour stages, type of delivery (Caesarean or vaginal delivery), the need for oxytocin use, the first- and fifth-minute Apgar scores, childbirth satisfaction and side effects will be recorded in the data collection form. The primary outcome will consist of Bishop score and duration of the first stage of labour, while other outcomes will be considered as secondary outcomes. Controlling the course of labour and decision-making for other interventions will be done routinely.

3.2.9 | Data collection tools

Data collection tools in this study include labour induction calculator (LIC), demographic and obstetric characteristic questionnaire, Bishop scoring table, birth satisfaction scale, partograph and labour stage checklist will be used.

Labour induction calculator (LIC)

This checklist which consists of maternal height, BMI, parity, gestational age and modified Bishop Score was first validated in the United States in 2018. It is standardized and is used for developing and validating the nomogram for the US population (Levine et al., 2018).

Demographic and obstetric questionnaire

This questionnaire includes items on age, marital status, level of education, employment status, level of income, number of pregnancies, and history of pregnancy and labour.

Bishop scoring table

One of the quantitative methods (measurable) for predicting the outcomes of labour induction is the scoring system described by Bishop in 1964. Cervix ripeness is calculated based on Bishop scoring system, which is measured on the ground of dilation, effacement, consistency, cervix position and the station of the presented part, whereby a score between 0–13 is allocated. With reduction in the Bishop score or decline of the cervix ripeness, the success rate of induction for achieving vaginal delivery also decreases. Bishop score 4 implies high probability of induction success. Most physicians state that if a woman has the following conditions, labour induction will be successful: cervix with 2 cm dilation, 80% effacement, soft consistency, being in the middle position and foetal presenting part in

TABLE 2 Bishop scoring table

Cervical status	Scoring			
	0	3	2	1
Position	Posterior	---	Anterior	Mid-position
Consistency	Firm	---	Soft	Medium
Effacement (%)	0%–30%	≥80%	60%–70%	40%–50%
Dilation (cm)	Closed	≥ 5 cm	3–4 cm	1–2 cm
Station	–3	+1, +2	–1, 0	–2

+1 station. There is disagreement over the score to be assigned as unripe cervix; different studies have considered a score between 4–5 as unripe cervix. However, concerning the research objectives, Bishop score 4 or less indicates unripe cervix and is considered an indication for preparation of the cervix (Navve et al., 2017) (Table 2).

Birth Satisfaction Scale-Revised (BSS-R)

It was developed by Martin et al. in 2014 to measure the extent of parturient satisfaction with the delivery experience. In order to determine the satisfaction with delivery, it will be completed 12–24 hr postdelivery. It includes 10 items based on 5-point Likert scale (in items 1, 3, 5, 6, 9 and 10, score 4 represents absolutely agree, while score 0 indicates absolutely disagree; on the other hand, in items 2, 4, 7 and 8, it is opposite, with score 0 indicating absolutely agree and 4 showing absolutely disagree). Score 0 represents no satisfaction while score 40 indicates maximum satisfaction. This scale has three subscales including experience of stress during labour (items 1, 2, 7 and 9), women's characteristics (items 4 and 8) and quality of care (items 3, 5, 6 and 10) (Martin & Martin, 2014). The psychometrics of this instrument have been measured by Nahae et al. in Iran, and this paper is under review.

Partograph

Partograph is an instrument which indicates the labour progression, whereby labour progression, maternal vital signs, foetal heart rate, pharmacological interventions, cervical dilatation, effacement, station, status of amniotic fluid, as well as the number and duration of contractions can be recorded (Lavender et al., 2018).

Labour stage progress checklist

It will be completed based on the notes recorded in the mother's files.

In order to determine the reliability of Bishop Score measurement, inter-rater reliability (IRR) method will be used. For this purpose, the Bishop score will be determined through vaginal examination by the researcher and one of the members in the ward on 10 pregnant women meeting the inclusion criteria. Thereafter, its correlation coefficient will be calculated. In order to determine the validity of the demographic and obstetric characteristic questionnaire, content and face validity will be applied. Further, the reliability of the birth satisfaction scale will be determined through

test-retest method on 20 women alongside determining the intraclass correlation coefficient (ICC), and internal consistency (Cronbach alpha coefficient).

3.2.10 | Data analysis and interpretation

In this phase, the data will be analysed by SPSS 24 through one-way analysis of variance and chi-square. In this study, $p < .05$ will be considered significant.

3.2.11 | Ethical considerations

This study was approved by the ethical committee of Tabriz University of Medical Sciences (Ethics code: IR.TBZMED.REC.1399.141). Written informed consent will be taken from all participants in both phases. The participants will be sufficiently assured about the confidentiality of their personal information when reporting the results. It would also be explained that they can quit the intervention at any time of research, and their withdrawal from the study is absolutely free, whereby absolutely no changes will occur in provision of routine services to them. The results would be provided to them if they wished.

4 | DISCUSSION

Induction of labour after 41 weeks reduces the risk of perinatal mortality. For this reason, many physicians today perform labour induction in 41-week low-risk pregnancies. They believe that induction of labour in such cases is a therapeutic policy to reduce the mortality and prevent increasing maternal complications (Bleicher et al., 2017; Jochum et al., 2019; Khooshideh et al., 2017). Meanwhile, determining the Caesarean delivery risk following labour induction is an important measure to reduce the emergency complications of unsuccessful induction. Perhaps, not inducing labour in high-risk Caesarean delivery cases may be an economical measure to reduce morbidity and mortality (Levine et al., 2018). Thus, in the first phase of the study, the Caesarean delivery risk estimation nomogram will be investigated and localized.

Decision-making on the method of labour induction should be based on different factors including safety, cost-effectiveness and expectations of pregnant women (Thies-Lagergren et al., 2013). Concerning the importance of labour induction along the policies of the WHO emphasizing reduction in Caesarean delivery, whose value is very high in our country, the use of novel effective and low-risk methods and drugs is always of interest (Kalati et al., 2018; Shahali et al., 2018). On the other hand, there is deficiency of information and inadequate clinical evidence on application of evening primrose oil in preparation of the cervix and labour induction. The available papers have used various methods of use and different drug doses with a wide range of bias, low quality and contradictory results (Simon

et al., 2014; Ty-Torredes, 2006). In the second phase, the research team intends to compare the effects of 4,000 mg vaginal EPO, CRB and misoprostol. In this way, in case of desired effectiveness, a cost-effective method with minimal side effects could be proposed.

4.1 | Strengths and limitations

One of the strengths of this research is that it will be performed on both nulliparous and multiparous women in 3 academic and non-academic hospitals. Double-blind method for intervention is another strength point of this study. Also, the Caesarean delivery risk estimation nomogram will be validated in Iran for the first time. Concerning the absence and non-use of such an instrument in our country, its application and localization for the first time in our country will be an important innovation for post-term pregnancy management. EPO, in case of desired effect, can also improve the results of labour induction and reduce the complications of misoprostol including uterine tachysystole. Meanwhile, unlike misoprostol, there is no necessity to hospitalize the mother or monitor the foetus constantly. It can even be used by the mothers themselves in an outpatient way. The CRB balloon allows for a completely mechanical dilation and does not require traction so it yields the same results with less pain compared with Foley catheter.

4.1.1 | The limitations of this research are follows

This predictive model is limited to the women who meet inclusion criteria for our study and may not be generalizable to women who do not fit these criteria. For example, it is not recommended this calculator be used in women with a prior Caesarean, women with ruptured membranes or women with a favourable cervix as the predictive ability in those populations is not known. Another limitation of this model is the inability to reliably predict Caesarean with 100% accuracy. However, given the fact there will always be confounding by indication and provider clinical decision-making that leads to perform a Caesarean delivery, achieving 100% accuracy in a prediction model like this would not be realistic. Because of the nature of the cook balloon, the participants and those implementing intervention cannot be blinded which may induce some performance bias. As EPO will be compared with misoprostol which is not permitted to be used in outpatients, we cannot use EPO in outpatients before admission, so it may take much more time to ripen the cervix in admitted pregnant women, it is recommended to use EPO in another research the day before admission.

5 | CONCLUSIONS AND IMPLICATIONS

This calculator can be used to augment patient counselling for women undergoing an induction with an unfavourable cervix. According to results of second phase, a non-harmful herb will help

delivery ward staff prepare mothers for good vaginal delivery and reduce unplanned Caesareans due to inductions with unripe cervix. It is recommended to use EPO on outpatients the day before admission and compare results with this study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

MM, FA, SMAC, MAJ and SHH: contributed to the design of the protocol. MM, FA and SHH: contributed to the implementation and analysis plan. MM and SHH: wrote the first draft of this protocol article, and all authors critically read the text and contributed to inputs and revisions, and eventually all of them read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Mojgan Mirghafourvand  <https://orcid.org/0000-0001-8360-4309>

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