Prevalence and risk factors associated with preterm birth in India: Systematic review and meta-analysis

Thangjam Devi[1] and Huidrom Singh[2]

[1]Affiliation not available
[2]Manipur University

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Abstract

Background: Preterm birth (PTB) is one of the important health concerns and a leading cause of infant mortality and morbidity worldwide. Objective: To investigate the potential and absolute risk factor(s) associated with PTB and also to understand the overall trend of the prevalence rate of PTB among the Indian population. Materials and methods: Search from PubMed, Medline, Google Scholar and web of science databases were included in assessing prevalence rate of PTB as well as evaluating association between various risk factors and preterm birth. Results: The prevalence rate of PTB is varied across the country and it ranges from 2% to 25.6%. The overall pooled risk of PTB varies with different risk factors such as gestational hypertension shows 19.16% (95% CI 8.54 to 29.78, I2 = 84.09 %); 9.49% for gravida (95% CI 2.99 to 16.00, I2 = 86.07%), 8.34 % for anaemia (95% CI 4.45 to 12.24, I2 = 79.88%)]; 8.34% for prior preterm birth (95% CI 4.45 to 12.24, I2 = 94.89%)] and4.61% for gestational diabetes (95% CI 1.48 to 7.73, I2 = 53.27%)];. Moreover, low socioeconomic status, inadequate antenatal care, infections during pregnancy, and advance maternal age, are also found to be potential risk factors of PTB among the Indian population. Conclusions: The rate of PTB in Indian population is above the rate estimated by WHO. Most of the etiological factors of PTB are modifiable and hence giving community awareness on its ill effects and preconception counselling should be emphasize to address the health consequences of PTB.

Introduction

The term preterm birth (PTB) is defined by World Health Organization (WHO) as babies born alive before completions of 37 weeks of gestational age [1]. In the early days, the determination of prematurity relied on birth weight. The low birth weight (LBW), with less than 2300 or 2500 grams, was considered for describing prematurity [2]. It is sub-categorized based on the gestational age such as extreme preterm (less than 28 weeks), very preterm (28 to 32 weeks), and moderate to late preterm (32 to 37 weeks) [1]. Moreover, preterm birth can also be sub-classified into two broad subtypes based on its cause such as spontaneous preterm birth and provider-initiated preterm birth. The spontaneous preterm birth occurs after spontaneous onset of labor following prelabour premature rupture of membranes whereas, the provider-initiated preterm birth occurs as induction of labor or elective cesarean delivery before 37 weeks of gestation for maternal or fetal indications or non-medical reasons [3]. According to the born too soon report published by WHO (2012), estimated that 15 million babies are born too early every year. Premature birth is one of the leading causes of neonatal morbidity and mortality in children below 5 years of age. Approximately 1 million children die each year due to complications of preterm birth [4]. Across 184 countries, the rate of preterm birth ranges from 5% to 18% of the babies born [5]. In developed and developing countries, medically unnecessary inductions and cesarean section deliveries before full term also increase preterm birth rate. The actual rate of preterm birth remains unexplained in many countries [4,6]. Sub-Saharan Africa and South Asia account for over 60% of preterm births worldwide. In India, 3,341,000 babies are born too early from the expected date [8], and 361,600 children under five years of age die due to complications associated with preterm birth. According to Indian

Foundation for Premature Babies (2013), India contributes 23.6% of the global preterm births, of which 13% are live preterm births (babies born <37 weeks), and 28% are with low birth weight [7, 8], and babies born per year <28 weeks are165,800 in India [7,8]. Studies have reported that in India 33,41,000 babies were born preterm per year, the ratio of boys to girls born preterm is 1.23, impaired preterm survivors per year are 80,700, and direct preterm child death per year are 3,61,600 [3,7,8]. According to every preemie scale report of India [8], hypertension (25%), anemia (55%), and diabetes (9%) are found to be significant risk factors that contribute to preterm birth. Though, further studies are required to understand the aetiology of PTB as it is a complex and multifactorial in nature. However, limited studies have been conducted in India to explore the possible risk factors that contribute to PTB. Moreover, most of the available literatures were confined only to some particular regions of the country. Therefore, the present systematic review and meta-analysis was carried out to investigate the potential and absolute risk factor(s) associated with preterm birth from the available literatures to control and take preventive measures in time. Moreover, an attempt was also made to understand the overall trend of the prevalence rate of preterm birth in India

Materials and Methods

Search of relevant literatures

A systematic search for original research articles published in the electronic databases such as PubMed, Medline, Web of science and Google Scholar was conducted from 2012 to 2019, which publishes research articles in English language. The keywords used for searching literatures included "Preterm birth, "India" in combination with "prevalence," "associated risk factors," and "outcomes." In the last 8 years, a total of 30 research articles were found published on the prevalence of preterm birth among different population groups of the country. Research papers that are published in non-English languages, seminar/conference, proceedings and dissertation, and thesis were excluded in the present study.

Inclusion Criteria

Articles were included if (i)the primary exposure of interest was the presence of risk factors like gestational hypertension, gestational diabetes, anaemia, gravida and prior history of preterm birth, (ii) the outcome of interest was preterm birth, which was defined as delivery at <37 weeks gestation, (iii) odds ratios (ORs) with their corresponding 95% confidence intervals (CIs) or standard errors were reported. Titles and abstracts were screened to exclude duplicates and ineligible studies. Moreover, we examined the full-text papers of the remaining records to confirm that the retrieved reports met our inclusion criteria and to extract data for the review (Figure 1).

Data Extraction

The following data have been extracted from the articles included in the present study - the name of the first author, year of publication, study design, sample size, follow-up period, associated risk factors, ORs and corresponding 95% Cis.

Statistical analysis

A random effect-model was used to estimate the pooled prevalence of the associated risk factors of preterm birth using MS-Excel [9]. I^2 statistics was also calculated to describe the variations among various studies caused due to its heterogeneity [10].

Results

On the whole, database searches identified 30 research articles from different electronic sources published from 2012 to 2019. Of which, 18 full-text research articles were included for systematic review and Only 9 research articles were included for meta-analysis to estimate the effect of the potential and absolute risk factors on preterm birth as well as to understand the overall trend of preterm birth in the Indian population.

It is evident from the available literature that the incidence of preterm birth is more frequent in developing countries like India than in other developed countries [7]. In general, the prevalence rate of preterm birth is

significantly high among the Indian population (15%), which is also found to be above the prevalence rate estimated by WHO [11]. Most of the available studies are concentrated only on some particular states of the country. It has not been explored in most of the Indian population. Moreover, the rate of prevalence of preterm birth reported in India varies greatly. In general, its frequency ranges approximately from 2.0% to 28.25% (Table 1). The highest frequencies were reported from Gujarat (25.6%) [12] and Karnataka (28.25%) [13]. According to the available data, it is evident that the degree of prevalence of PTB also varies within the state of Uttar Pradesh ranging from 18.4% to 25.6% [12,14,15]. The lowest rate of preterm birth is reported from Goa (7.81%) [16] and Maharashtra (6.1%) [17]. Regarding the types of preterm births and its prevalence, a study conducted among women in rural communities near Nagpur, Central India reported high rates of moderate to late preterm births (67%), very preterm (22%) and extreme preterm (11%) [18]. Other similar studies also revealed a high prevalence rate of extreme preterm birth with 60% in Punjab, 15.6% in Gujarat, and 7% in Haryana [18,19,20]. The highest frequency of very preterm birth is reported from Gujarat (52.6%).It is followed by Haryana (38%) and Punjab (22%), whereas, the moderate to late preterm birth frequencies are highest in Haryana (55%),which is followed by Gujarat (31.6%) and Punjab (18%) (Figure 2). The incidence of preterm birth in India was examined using the available data published during the year 2012 to 2019. The data on the prevalence of preterm

Preterm Birth and Risk Factors birth indicates an increasing trend during the last eight years (Figure 3).

A total of 18 research articles published during 2012 to 2019 were reviewed for understanding the potential risk factors of preterm birth in the Indian population. Most of the studies were concentrated only on some particular states of the country. It has not been explored in most of the Indian population. The available research works were mainly carried out in Gujarat, Karnataka, Maharashtra, Tamilnadu and Uttar Pradesh; and limited studies have also been reported from some of the other states like Goa, Haryana, and Punjab. Different study designs have been adopted to understand the risk of preterm birth which includes hospital based studies, case-control studies, community based studies, and longitudinal cohort study methods; and majority of the studies were published during 2016 and 2017. Various numbers of risk factors have been reported by different studies associated with preterm birth. Such risk factors could be broadly categorized into two major groups based on its nature of risk such as modifiable and non-modifiable groups. Each group consists of various sub-groups with different a number of risk factors. The modifiable risk factors of preterm birth include mother's behaviour at the time of pregnancy, educational status, socio-demographic factors, socio-economic status, nutritional status and medical history of illness. On the other hand, the non-modifiable risk factors are those factors such as pregnancy induced medical conditions, infection during pregnancy and pregnancy history of the mother.

The risk of preterm birth has been shown to be associated with various maternal health conditions induce during pregnancy. Pregnancy induced hypertension is one of the commonest medical conditions causing preterm birth as reported in most of the studies conducted in India. It has been evident that pregnancy induced hypertension as the commonest (21.45%) obstetrical risk factor of preterm birth among the Southern Indian population [21]. Moreover, the risk of preterm birth shows more than the threefold increased risk among mothers experiencing pregnancy induced hypertension (OR=3.23, CI 1.85-5.63). Such positive association have also been reported from different population groups by different studies [13,14,18,19,27]. It is followed by gestational diabetes, which shows a significant increase risk of delivering preterm babies. Community based longitudinal studies conducted among the rural population of Mysuru have revealed a strong positive association between mother with gestational diabetes and preterm delivery (OR=11.8, CI 1.11-125.41) [22]. The association of gestational diabetes with preterm birth is also evident from various studies [13,18,27,23]. The premature rupture of membrane (PROM) before the onset of labor, one of the common complications of pregnancy, is also reported to be significantly associated with preterm birth by various studies [13,14,19,20,30]. Abnormal volume of amniotic fluid during gestational age such as oligohydramnios and polyhydramnios are shown to be linked with preterm birth[13,19,23,27]. In addition to the above risk factors of preterm birth, there are other pregnancy related medical conditions which have also been reported to be a risk for preterm birth different studies such as threatened abortion, idiopathic, hypothyroid, antepartum haemorrhage, malpresentation, and uterine over distension [16,21,24,27,30]. More-

over, multiple pregnancy that is pregnancy with more than one baby at a time such as multiparity [14], and multiple gestation [13,16,21] are also reported to have a significant relationship with preterm birth.

The available literature indicate that pregnancy history of a woman can also be helpful in predicting the possibility of preterm delivery. For example, mothers having a prior history of preterm delivery are most likely to give preterm birth babies as compared to mothers with term birth delivery. The odds of delivering premature is significantly high with prior preterm birth (OR=5.11; 95% CI 1.67-15.61) [18]. Similar findings was also reported with significant increased risk of preterm birth among mothers with the earlier history of preterm delivery [19,20,23,25,26,27,29]. It is also evident from the literature that pregnancies for the first time (both primigravida and elderly gravida) are also more likely to deliver preterm birth babies [14,17]. On the other hand, the history of abortion [18,20], intrauterine death, previous stillbirth, and previous CS are also reported to be at higher risk of preterm delivery [22,30]. Moreover, the study reported that delivery via caesarean section had increased the rates of preterm birth indicating a high induction of labor [14].

Infection during pregnancy or having an earlier history of infection can cause severe consequences to both fetus and mother. According to the available literatures, it is evident that vaginal infection and urinary tract infection are the common forms of infections associated with adverse pregnancy outcomes causing various complications including preterm birth [16]. Such positive association has been further supported by a study carried out in Gujarati population which shows higher odds of preterm birth among the mothers with urinary tract infection (OR= 3.28, 95% CI 1.15-9.35), bacterial vaginosis (OR=5.29, 95% CI 2.49-11.23) and other infections too such as fever (OR=8.6, 95% CI 1.04-69.05) [18]. Similar findings have also been reported from Jalandhar [19] and Haryana [20]. On the other hand, pregnant women with periodontitis (a severe form of gum infection) are also reported to have a higher risk of preterm birth delivery [23,28].

Maternal anthropometric indicators such as height, weight, body mass index (BMI), nutritional status have been considered as important factors in association studies screening and detecting women at risk of adverse pregnancy outcomes. Pregnant women having low body mass index (BMI) before pregnancy are reported to be at higher risk of delivering preterm babies [27]. According to the South Indian study [21], mothers with height <1.50mshowed more than one fold significant increased risk for preterm birth delivery (OR=1.96, CI 1.12-3.42). Similar finding have also reported the risk of preterm birth among mothers with height <1.50 m (ARR=2.21, CI 1.1-4.1) [23]. However, inconsistent results are also reported by different studies indicating no significant association between maternal height (<1.50m) and preterm birth [18]. Maternal nutritional status before and/or during pregnancy have been playing a crucial role in fatal development as well as successful pregnancy outcome. The incidence of preterm birth was significantly much higher among the malnourished mother as well as mother having different degrees of anaemia [26].

Studies have revealed that anaemia during pregnancy can lead to adverse pregnancy outcomes including premature birth, low birth weight and an even higher chance of maternal mortality. The condition may be more critical when the mother had a history of anaemic condition before pregnancy. Hospital based study in Assam showed that lower estimates of haemoglobin level are at higher risk of delivering preterm birth and low birth weight babies [31]. Other studies have further revealed that maternal anaemic condition is significantly contributed to preterm birth delivery among Tamilnadu and Gujarat population [13,32]. Conflicting findings have also been reported that maternal anaemic condition has no significant association with preterm delivery [17,31]. On the other hand, low intake of folate supplement during pregnancy also shows increases risk of preterm birth in the South Indian population [32].

Education plays an important role in successful and good pregnancy outcomes. Studies have shown that a mother's educational status have a positive relationship with the outcome of pregnancy. Illiteracy and mothers with low educational status are more likely to deliver preterm babies than a mother having with higher educational status [12,15]. Regarding socio-economic status, various studies have shown consistent positive associations between mothers with low socio-economic status and preterm delivery. Mother with poor economic status has a higher possibility of having preterm birth (OR=2.02, CI 1.18-3.45) [18]. Majority of the rural women population who delivered prematurely belongs to the poor socio-economic class [24,29]. It is also evident that women living in joint families, having monthly income [?]Rs 2999/-, maternal illiteracy

and those who are housewife are more at higher risk for preterm birth [12,15].

Maternal age is one of the most significant modifiable risk factors associated with preterm birth. Both early and advanced maternal age is reported to have adverse pregnancy outcome as evident from different studies. In a retrospective hospital-based study conducted in the Marathwada region of Maharashtra showed higher odds of preterm delivery in women younger than 22 years of age than in older women at the time of delivery (OR=3.23 CI 1.36 - 7.65, p=0.008) [17]. The risk of delivering low birth weight baby was twice as high as in mothers who were <22 years of age at the time of delivery (OR=2.03 CI 1.14 - 3.60, p=0.02) [17].It is further supported by another study[33] reporting teenage mothers (maternal age [?]19 years) were more likely to deliver preterm and a low birth weight baby. These findings are consistent with the findings of studies conducted in North-East India that shows a higher incidence of preterm deliveries among the adolescent mother (OR=1.6 CI 1.1 - 2.6) [34]. Moreover, the advanced maternal age (40 years and above) was also shown to be associated with an increased risk of preterm birth [15,26]. Thus, available literature show that maternal age has significant role in delivering preterm birth. Further, paternal age has also been reported to be associated with preterm birth. Community based longitudinal study carried out in rural Mysuru population of Karnataka showed 7 fold increase risk of preterm birth with an increase in the age of father [22]. All these findings suggested that not only maternal but also paternal age contribute to the risk of preterm birth.

Regular and timely antenatal check-up are the key important factor in preventing any kind of unwanted pregnancy outcomes. It is evident that most of the mothers who gave preterm birth deliveries had never sought antenatal care [14,19]. The results are consistent with the study [18] that also reveals high odds of preterm birth among those mothers who have inadequate antenatal care (OR=1.90 CI 1.13-3.18). Moreover, it is also observed that behaviours of the mother during pregnancy such as long term sleep and sexual intercourse during any trimester are more likely to deliver preterm birth babies [28].

Meta-analysis Results

The search returned 30 articles, of which 9 articles met all of the inclusion criteria for full-text review in the quantitative meta-analysis involving 18,470 women. The included studies were almost entirely case control studies and cross sectional studies [12,15,16,21,27,29], with only one cohort study [28].

The risk of preterm birth has been associated with various pregnancy induced maternal health conditions like gestational hypertension and gestational diabetes. A total of 5 studies published during the year 2014 to 2018 were included for estimation of pooled prevalence of associated gestational hypertension with preterm birth [13,21,22,23,27]. The sample size of the studies ranges from 246 to 4137 giving a total of 6158 samples. The risk of preterm birth delivery due to gestational hypertension ranges from 2.03% to 61.49%. The pooled risk is 19.16% for gestational hypertension with $I^2 = 84.09\%$ (95% CI 8.54 to 29.78) (Figure 5A). Moreover, for the risk factor gestational diabetes, 4 studies published during the year 2015 to 2017 were included for the estimation of pooled prevalence [12,18,23,27]. The risk of preterm birth among mothers with gestational diabetes ranges from 2.03 % to 7.72%. The pooled risk of preterm birth among women with gestational diabetes was 4.61% (95% CI 1.48 to 7.73) with and $I^2 = 53.27\%$ (Figure 5B).

One of the strongest clinical risk factors for preterm birth is having a prior history of preterm birth. Women with a history of previous preterm birth delivery was reported significantly associated with preterm birth [19,20]. Out of 9 studies, four reported the prevalence of preterm birth with associated risk factors prior preterm birth in India with a total number of sample size is 8035 published during the year 2015 to 2017 [18,19,23,27]. The risk of preterm birth among women with prior history of preterm delivery ranges from 5.23% to 50.0%. The pooled risk of preterm birth was 8.34% (95% CI 4.45 to 12.24, $I^2 = 94.89\%$) for mothers having prior history of preterm delivery (Figure 5C).

Anaemia is one of the major health issues in India, particularly among pregnant women. Four studies reported the overall risk of anaemia at <37 weeks of gestation with a total number of sample size is 5746 published during the year 2014 to 2018[12, 17, 21, 22].The risk of preterm birth ranges from 2.03% to 46.1% among those mothers having anaemia was 8.34 % (95% CI 4.45 to 12.24, $I^2 = 79.88\%$) [12,17,21,22](Figure

5D).Regarding gravida, it includes 4 studies published during the year 2015 to 2018, reporting association of preterm birth with gravida with a total of 14,021 samples[12,16,17,27]. The risk of preterm birth ranges from 5.23% to 25.36%. The pooled risk of preterm birth among the Indian population was 9.49% for gravida with I^2 = 86.07% (95% CI 2.99 to 16.00) (Figure 5E).

Discussion

Main Findings

The present systematic review and meta-analysis, which included 18 studies representing 18,470 women, provides an overview of the overall potentialand absolute risk factor(s) associated with preterm birth and also to understand the overall trend of the prevalence rate of preterm birth among the Indian population. The selection of studies was based on a clearly defined search strategy. The World Health Organization estimates the prevalence of preterm birth from 5 to 18% across 184 countries, of which the highest rates are reported in sub Saharan Africa and South Asia [1].The present review provides the current trends on the prevalence of preterm birth in India. The overall incidence of PTB rates in India is found to be above the level (15%) estimated by World Health Organization [11]. Moreover, the incidence of preterm birth is varied across the country and it ranges from 2% to 25.6%. The prevalence rate of preterm birth in India is above the other studies reported from different parts of the world population. The rate of PTB reaches upto 18.3% in Kenya and 14.2% among the Tanzania population [35,36]. The rate of PTB prevalence in Taiwan increased from 8.2% in 2001 to 9.1% in 2011 [37]. The lowest prevalence rate of PTB was reported from Abu Dhabi with (6.3%) and Iran (5.1%) which is above the lowest rate of PTB in the Indian population [38,39].

The data presented in the review also focuses on several risk factors related to preterm birth, particularly in the Indian population. The potential risk factors found to be associated with PTB reported by different studies conducted in India includes having prior history of preterm birth, pregnancy induced hypertension, preterm rupture of the membrane, gestational diabetes, infections (urinary, vaginal, etc), inadequate antenatal care, poor socioeconomic status, maternal age (teenage and advance), polyhydramnios, anaemia, malnutrition, multiple gestation, oligohydramnios and so forth (Figure 4). The findings of the present review show similar findings when compared with other studies reported from outside India. In a study conducted in Kenya reported that maternal age, previous preterm birth, multiple gestation, pregnancy induced hypertension, prolonged prelabour rupture of membrane, and urinary tract infections were significantly associated with preterm birth (p=<0.05) [36]. Hospital based study in Brazil indicates that multiple pregnancies and inadequate prenatal care have been indicated as a risk factor for preterm birth [40]. Furthermore, prior history of preterm birth increased the chance of preterm birth delivery by 23% among Brazilian women. Maternal medical complications, maternal age <20 years or [?]40 years were positively associated with an increased risk of preterm delivery [37]. Moreover, preterm births were almost two times more likely among black women with pregnancy-induced hypertension (OR = 1.8; 95% CI 1.5 to 2.2) [41]. In a study conducted in California, urinary tract infections increase a woman's risk of preterm birth delivery [42]. In another case-control study reported from Cyprus, poor socioeconomic status along with stress, prolonged working hours and advanced maternal age at childbirth were associated with increased odds of preterm delivery [43].

To our knowledge, this is the first systematic review and meta-analysis to examine the national estimate of preterm birth in India. The overall pooled prevalence of association between gestational hypertension and preterm birth was19.16% (95% CI 8.54 to 29.78, I^2 = 84.09 %) in the present study. The finding is consistent with a previous review conducted in the Ethiopian population reporting 4.69% risk with I^2 67.6% among mothers who had gestational hypertension (95% CI 2.32 to 9.49) [44].

Similarly, a systematic review and meta-analysis study, found that the risk of preterm birth with the previous history of PTB was 30.0% (95% CI 27 to 34, I^2 = 98.6%) indicating between-study heterogeneity [45]. It supports the findings of the present study in which the pooled risk of preterm birth was 8.34% with I^2 94.89% among mothers having a history of PTB delivery (95% CI 4.45 to 12.24) which is also observed to be high in heterogeneity. Regarding maternal anaemia and its association with preterm birth, Rahmati *et al* revealed that maternal anaemia during pregnancy increases the risk for premature birth with a relative

risk of 1.56 (95% CI, 1.25 to 1.95) [46]. Similarly, a meta-analysis that conducted among the low and middle income countries including 13 studies showed significantly greater risk of preterm birth in anaemic pregnant women (RR=1.63, 95% CI 1.33-2.01, I^2=88%) [47]. Our results confirm the consistent findings with previous meta-analysis [44,45,46,47] showing that pregnancy induced hypertension, prior history of preterm birth, maternal anaemia was associated with preterm birth. In addition, the present meta-analysis also found that gestational diabetes and gravida are potential risk factors of preterm birth which have not been reported in the previous studies. Taking into consideration the overall pooled risk and its heterogeneity I^2 values, pregnancy induced hypertension, gestational diabetes, prior history of preterm birth, maternal anaemia and gravida, could have higher risk of preterm birth in Indian population.

Strength and Limitations

Strengths of our systematic review and meta-analysis include a thorough and systematic search of multiple databases, so it is likely that all the relevant publications were identified. The present study provides a reference target of what evidence already exists for each associated risk factors and charts out the direction in which further research is needed from an Indian perspective. Since there has been no similar previous study, this review and meta-analysis showed the national pooled prevalence of the effect of absolute risk factors like pregnancy induced hypertension and diabetes, prior history of preterm birth, maternal anaemia and gravida on preterm birth in India.

Limitations include the fact that search strategy was limited to articles published in English only, and this could lead to the risk of publication bias. There are a limited number of studies performed on preterm birth in India. Moreover, the places of the study were restricted to only a few states of India and the limited number of literatures was also found from the North-Eastern region of India (Figure 2). However, several limitations should be considered as the included studies were not representative of the entire country. Most of the studies were carried out in the Southern and Northern parts of the country. Studies included in the meta-analysis should be considered as weak in quality (n = 9). Several other studies were excluded to consider in this meta-analysis due to unclear reporting by authors. Although, several numbers of studies were able to identify the prevalence of preterm birth and most did not identify the association of various risk to PTB. As a consequence, many other potential risk factors could not be pooled and all of the existing evidence could be summarised in the meta-analysis. Further, relevant predictors might have been missed; hence future research should include other factors of preterm birth to explore the in-depth on the subject of inquiry.

Implications and Future Directions

The present study, being a first of its kind, might raise a number of important implications for future research and clinical practice. More research will in fact be necessary to refine and further elaborate the outcomes of the present review. The earliest study in our review was published in 2012 [24], and most were published between 2016 and 2018.However, limited studies were reported from 2019. Thus, the findings of this systematic and meta-analysis can be used to identify the most significant risk factors to target and gaps in care to detect and implement solutions for better-quality outcomes. Further, updating systematic literature reviews might define the research gaps and propose new interventions to reduce various risk factors during pregnancy. Moreover, innovation in conducting research in a specific population that are most affected by preterm birth might decrease the overall rate of preterm birth. Moreover, population specific research studies should be encouraged to focus researchers in addressing the unanswered issues that matter most to women at high risk for preterm birth.

Conclusion

The present systematic review and meta-analysis reaffirmed that preterm birth is significantly associated with many potential risk factors such as socio economic status, health services, socio-demographic, anthropometric and nutrition, infection, pregnancy induced complication, pregnancy history, history of illness, education and behaviour. The high incidence of preterm birth could be reduced to some extent by providing proper antenatal care to pregnant women who are at higher risk. The dynamic approach, combined with the

involvement of primary as well as tertiary health sectors, can help in achieving the goal of reducing PTB in India. The data specified in the present review could also be used to grasp attention to decrease the frequency of preterm births and its consequences in India. Moreover, the result could provide policy makers, clinicians, and expectant parents to reduce the chances of delivery prematurely.

Disclosure of Interests

None declared.

Contribution to authorship

TCD designed the study and HSS provided important feedback on the purposed study design

TCD screened all abstracts, reviewed full articles and performed data extraction for the purposes of meta-analysis. TCD also conducted the systematic literature search and quality assessment. TCD drafted the initial manuscript, which was thoroughly reviewed for important intellectual content and revised by all authors (TCD and HSS). All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Details of ethics approval

Not applicable.

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References

1. Howson CP, Kinney MV, Lawn J. Born Too Soon: the global action report on preterm birth March of Dimes, PMNCH, Save the Children, WHO 2012.
2. Behrman RE, and Butler AS. Preterm Birth: Causes, consequences, and prevention. Washington, D. C.: National academies press (US); 2007.
3. Liu L, Oza S, Hogan D, Chu Y, Perin J, Chu Y, Perin J, Zhu J, Lawn JE, Cousens S, MathersC, Black RE. Global, regional, and national causes of under-5 mortality in 2000-15:an updated systematic analysis with implications for the Sustainable Development Goals. *Lancet*2016; 388:3027-35
4. Born too soon. The Global Action Report for Preterm Birth, MoD, PMNCH, Save the Children, WHO, New York, NY, USA, 2012.
5. WHO Preterm birth available at https://www.who.int/en/news-room/fact-sheets/detail/preterm-birth retrieved on dated 23 May, 2019.
6. Beck S, Wojdyla D, Say L, Betran AP, Merialdi M, Requejo JH, Rubens RM, Van Look PFA. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. Bull World Health Organ. 2010 Jan; 88(1):31-8.
7. Blencowe H, Cousens S, Oestergaard MZ. National, regional and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet* 2012;379(9832): 2162–72.
8. India-profile for Preterm birth and low birth weight prevention care. Available at https://www.healthynewbornnetwork.o content/uploads/India-1.pdf retrieved on 23 May,2019
9. NeyeloffJL, Fuchs SC, & Moreira LB. Meta-analyses and Forest plots using a microsoft excel spreadsheet: step-by-step guide focusing on descriptive data analysis. *BMC res notes* 2012;5(1):52.
10. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res synth methods* 2010;1(2): 97-111.
11. Vogel JP, Lee AC, Souza JP. Maternal morbidity and preterm birth in 22 low- and middle-income countries: a secondary analysis of the WHO Global Survey dataset. *BMC Preg Childbirth* 2014; 14:56.
12. Dayanithi M. Low birth weight and premature births and their associated maternal factors. *Int J Community Med Public Health*2018;5(6): 2277-85.

13. Kuppusamy N, Vidhyadevi A. Prevalence of preterm admissions and the risk factors of preterm labor in rural medical college hospital.*Int J Sci Stud* 2016;4(9):125-28.
14. Jamal S, Srivastava R. A retrospective analytical study of the epidemiology and causes of preterm birth. *Int J Reprod Contracept ObstetGynecol* 2017;6(12):5453-7
15. Singh S, Malhotra AK. Across-sectional study on prevalence of preterm birth in medical college Jhansi (U.P). Indian J Applied Res 2018; 8(10):50-52.
16. Fernandes SF, Chandra S. A study of risk factors for preterm labour.*Int J Reprod Contracept Obstet Gynecol* 2015;4(5):1306-12.
17. Ahankari A, Bapat S, Fogarty A, Tata L. Factors associated with preterm delivery and low birth weight: A study from rural Maharashtra, India. *F1000Research* 2017; 6:72.
18. Patel A, Prakash AA, Pusdekar YV, Kulkarni H, Hibberd P. Detection and risk stratification of women at high risk of preterm birth in rural communities near Nagpur, India. *BMC Preg Childbirth*2017;17(1):311.
19. Mahajan A, Magon S. Study of risk factors for preterm births in a teaching hospital: A prospective study. *Int J Med Den Sc* 2016; 6:1407-12.
20. Garg S, Kaur T, Saran AS, Yadav M. A study of etiology and outcome of preterm birth at a tertiary care centre. *Int J Reprod Contracept Obstet Gynecol* 2017;6(10): 4488-91.
21. Rao CR, de Ruiter LE, Bhat P, Kamath V, Kamath A, Bhat V. A Case-Control Study on Risk Factors for preterm deliveries in a secondary care hospital, Southern India. *ISRN Obstet Gynecol*2014.
22. Rashmi A, Narayanamurthy MR, Vidya GS, Vidyalaxmi K, Renuka M. Risk factors for preterm birth: a community based longitudinal study in rural Mysuru, Karnataka, India. *Int J Community Med Public Health* 2016;3(12):3576-80.
23. Tellapagadra C, Eshwara VK, Bhat P, Acharya S, Kamath A, Bhat S, Rao C, Nayak S, Mukhopadhyaya. Risk factors for preterm birth and low birth weight: A hospital-based prospective study. *J prev med public health* 2016; 49: 165-175.
24. Bangal V, Shinde K, Khanwelkar G, Patil N. A study of risk factors and perinatal outcome in preterm labour at tertiary care hospital.*Int J Biomed Res* 2012;3(3):147-50.
25. Patel PK, Pitre DS, Bhooker SP. Predictive value of various risk factors for preterm labor. *Natl J Community Med* 2015;6(1):121-5
26. Radhanpuri F, Desai DA, Sharma J, Kaur P. Preterm birth and its outcome. *Int J Reprod Contracept ObstetGynecol*2014;3(1):153-57.
27. Soundarajan P, Muthuramu P, Veerapandi M, Marriapam R. Retrospective study factors related to preterm birth in Government Raja Mirasudar Hospital and obstetric and perinatal outcome. *Int J Reprod Contracept Obstet Gynaecol* 2016;5(9):3006-10.
28. Trivedi P, Saxena D, Puwar T, Savaliya S, Ganguly P. A cohort study on risk factors for preterm births in rural Gujarat. *Indian J Public Health* 2019; 62:111-6.
29. Avachet SS, Kambale SV, Phalke BD. Determinants of preterm labour in a rural medical college hospital in Western Maharashtra. *Nepal J Obstet Gynaecol* 2013; 8(1):31-33.
30. Shetty MB, Krupa BM, Mounica M, Asha S, Davis SP, Suneha P. Preterm birth: associated risk factors and outcome in tertiary care center.*Int J Reprod Contracept ObstetGynecol* 2017; 6(8):3271-74.
31. Bora R, Sable C, Wolfson J, Boro K, Rao R. Prevalence of anemia in pregnant women and its effect on neonatal outcomes in Northeast India.*J Matern Fetal Neonatal Med* 2014; 27(9): 887-91.
32. Dwarkanath P, Barzilay JR, Thomas T, Thomas A, Bhat S, Kurpad AV. High folate and low vitamin B-12 intakes during pregnancy are associated with small-for-gestational age infants in South Indian women: a prospective observational cohort study. *Am J ClinNutr*2013;98(6):1450-8.
33. Mahavarkar SH, Madhu CK, Mule VD. A comparative study of teenage pregnancy. *J ObstetGynaecol* 2008;28(6):604-7.
34. Medhi R, Das B, Bas A, Ahmed M, Bawri S, Rai S. Adverse Obstetrical and Perinatal Outcome in Adolescent Mothers Associated with First Birth: A Hospital-Based Case-Control Study in a Tertiary Care Hospital in North-East India. *Adolesc Health Med Ther* 2016; 7:37-42.
35. Temu TB, Masenga G, Obure J, Mosha D, Mahande MJ. Maternal and obstetric risk factors associated

with preterm delivery with preterm delivery at a referral hospital in northern-eastern Tanzania. *Asian Pacific J Reprod* 2016; 5(5): 365-370.
36. Wagura P, Wasunna A, Laving A, Wamalwa D, Nganga P. Prevalence and factors associated with preterm birth at Kenyatta national hospital. *BMC Preg childbirth* 2018; 18:107.
37. Chen KH, Chen IC, Yang YC, Chen KT. The trends and associated factors of preterm deliveries from 2001 to 2011 in Taiwan. *Med* 2019; 98:13.
38. Taha z, Hassan AA, Ludmilla WS, Papandreous D. Factors associated with preterm birth and low birth weight in Abu dhabi, the United Arab Emirates. *Int J Environ Res Public Health* 2020; 17:1382.
39. Alijahan R, Hazrati S, Mirzarahimi M, Pourfarzi F, Hadi PA. Prevalence and risk factors associated with preterm birth in Ardabil, Iran. *Iran J Reprod Med* 2014;12(1): 47-56.
40. De Medeiros BKB, Cornetta MC, Crispim JO, cobucci RN. Risk factors associated with preterm birth in a Brazilian maternal and child health hospital. *Obstet Gynecol Cases Rev* 2018; 5:136.
41. Samadi AR, Mayberry RM. Maternal hypertension and spontaneous preterm births among black women. *Obstet Gynecol* 1998;91(6):899-904.
42. Baer RJ, Bandoli G, Chambers BD, Chambers CD, Oltman SP, Rand L, Ryckman KK, Jelliffe-Pawlowski LL. Risk of preterm birth among women with a urinary tract infection by trimester of pregnancy. *Am J ObstetGynecol* 2019; 220 (1), S433-S434.
43. Stylianou-Riga P, Kouis P, Kinni P, Rigas A, Papadouri T, Yiallouros PK, Theodorou M. Maternal socioeconomic factors and the risk of premature birth and low birth weight in Cyprus: a case-control study. *Reprod Health* 2018;15(1):157.
44. Mulualem G, Wondim A, Woretaw A. The effect of pregnancy induced hypertension and multiple pregnancies on preterm birth in Ethoipia: a systematic review and meta-analysis. *BMC Res Notes*2019;12(1):91.
45. Philips C, Velji Z, Hanly C, Metacalfe A. Risk of recurrent spontaneous preterm birth: a systematic review and meta-analysis. *BMJ Open* 2017;5;7(6).
46. Rahmati S, Azami M, Badfar G, Parizad N, Sayehmiri K. The relationship between maternal anaemia during pregnancy with preterm birth: a systematic review and meta-analysis. *J Matern Fetal Neonatal Med* 2019;1-11.
47. Rahman M, Abe SK, Rahman S, Kanda M, Narita S, Bilano V, Ota E, Gilmour S, Shibuya K. Maternal anemia and risk of adverse birth and health outcomes in low- and middle-income countries: systematic review and meta-analysis. *Am J Clin Nutr* 2016; 103:495-504.

Table 1: Studies on preterm birth and its risk factors among the Indian population

Author and year of publication (state)	**Study design**	**No of cases**	**No of Control**	**Prevalence (%)**	**Associated Risk factors**	***OR/*ARR with 95% CI**	**Outcomes**
Bangal et al, 2012 (Maharashtra) [24]	Prospective observational study	21	125	13.2	Antepartum haemorrhage, maternal anaemia, hypertension	-	Preterm labor, perinatal mortality

Author and year of publication (state)	Study design	No of cases	No of Control	Prevalence (%)	Associated Risk factors	*OR/*ARR with 95% CI	Outcomes
Avachet et al, 2013 (Maharashtra) [29]	Cross-sectional study	315	2105	15	Low socioeconomic status, urinary tract infections, prior history of preterm birth	-	Preterm labor
Rao et al., 2014 (Karnataka) [21]	Case-control study	154	334	5.8	Gestational hypertension	*3.23 (1.85-5.63)	Preterm birth, Low birth weight
					Height <1.50m	*1.96 (1.12-3.42)	
					Polyhydramnios	*1.90 (1.00-3.61)	
					Twin gestation	*7.60 (2.44-23.73)	
					Threatened abortion	*2.94 (1.30-6.63)	
Radhanpuri et al., 2014 (Gujarat) [26]	Retrospective hospital-based study	272	1599	17.01	Poor socioeconomic status, previous preterm birth, anaemia and Malnutrition, advanced maternal age,	-	Preterm birth

Author and year of publication (state)	Study design	No of cases	No of Control	Prevalence (%)	Associated Risk factors	*OR/*ARR with 95% CI	Outcomes
Fernandes et al., 2015 (Goa) [16]	Case-control study	410	250	7.81	Hypertensive disorders, antepartum haemorrhage, malpresentation, multiple gestations, UTI, and presence of vaginal infections.	-	Preterm birth
Patel et al. (2015) (Baroda, Gujarat) [18]	Prospective comparative study	120	120	EP- 15.6 VP- 52.6 MLP-31.6	Low socioeconomic status	*2.02 (1.18-3.45)	Preterm labor
					Prior preterm birth	*5.11 (1.67-15.61)	
					Prior second trimester abortion	*3.53 (1.25-9.99)	
					Inadequate antenatal care	*1.90 (1.13-3.18)	
					Maternal medical disorders (anaemia, Pregnancy induced hypertension, jaundice, cardiac disease, diabetes mellitus, tuberculosis etc)	*7.97 (4.32-14.69)	
					Uterine over distension	*31.31 (4.16-235.34)	

Author and year of publication (state)	Study design	No of cases	No of Control	Prevalence (%)	Associated Risk factors	*OR/*ARR with 95% CI	Outcomes
					Urinary tract infection	*3.28 (1.15-9.35)	
					Bacterial vaginosis	*5.29 (2.49-11.23)	
					CRP reactive (chorioamnionitis)	*6.36 (2.35-17.20)	
					Other infections (associated with fever)	*8.6 (1.04-69.05)	
Rashmi et al, 2016 (Karnataka) [22]	Community-based longitudinal study	5	246	2.0	Gestational diabetes mellitus	*11.8 (1.11-125.41)	Preterm birth
					Age of the father	*7.57 (1.47-38.99)	
					Previous stillbirths, Intrauterine death, Previous caesarean section	*5.76 (0.91-36.14)	
Kuppusamy et al., 2016 (Tamil-nadu) [13]	Retrospective hospital-based study	609	1547	28.25	Anaemia, PROM, Pregnancy-induced hypertension, oligohydramnios, multiple pregnancies, gestational diabetes mellitus	-	Preterm birth
Soundarajan et al., 2016 (Tamilnadu) [27]	Case-control studies	356	579	5.6	Prior preterm birth	*12.7 (3.9-40.4)	Preterm birth
					Hypertension	*7.3 (2.1-25.4)	

Author and year of publication (state)	Study design	No of cases	No of Control	Prevalence (%)	Associated Risk factors	*OR/*ARR with 95% CI	Outcomes
					Oligohydramnios	*3.9 (1.6-9.5)	
					Diabetics	*3.7 (1.1-11.8)	
					Prepregnancy low BMI	*2.0 (1.1-3.8)	
					Urinary tract infection	*1.8 (1.0-3.2)	
					Hypothyroid	*2.0 (1.0-3.8)	
Tellapagadra et al., 2016 (Karnataka) [23]	Prospective hospital-based study	61	790	7.8	Previous preterm delivery	**5.37 (1.5-19.1)	Preterm birth
					Periodontitis	**2.75 (1.1-4.9)	
					Oligohydramnios	**5.23 (2.4-11.5)	
					Presence of Nugent's intermediate vaginal flora	**2.75 (1.4-5.1	
					Gestational diabetes mellitus	**2.91 (1.0-8.3)	
					Maternal height <1.50 m	**2.21 (1.1-4.1)	
Jamal et al., 2017 (Uttar Pradesh) [14]	Retrospective analytical study	436	2128	18.4	Teenage mother, elderly gravidas, multiparity, inadequate antenatal care, PROM, Pregnancy-induced hypertension,	-	Preterm birth, high labor induction, and caesarean section rates

Author and year of publication (state)	Study design	No of cases	No of Control	Prevalence (%)	Associated Risk factors	*OR/*ARR with 95% CI	Outcomes
Ahankari et al., 2017 (Maharashtra) [17]	Retrospective hospital-based study	40	615	6.1	Maternal age	*3.21 (1.54-6.69)	Preterm birth Low birth weight
					Primigravida	*3.75 (2.21-6.37)	
Mahajan et al., 2017 (Jalandhar) [19]	Prospective study	100	100	EP- 60.0 VP- 22.0 MLP- 18.0	Preeclampsia, PROM, history of previous preterm births, genitourinary infections, polyhydramnios.	-	Preterm birth
Garg et al., 2017 (Haryana)[20]	Hospital-based study	100		EP-7.0 VP-38.0 MLP-55.0	Genitourinary tract infections, PROM, history of Preterm birth and abortions	-	Preterm birth
Shetty et al., 2017 (Karnataka) [30]	Retrospective cohort study	343	1904	18.01	Hypertensive disorder during pregnancy, PROM, idiopathic, and previous LSCS.	-	Neonatal mortality Stillborn
Singh et al. 2018 (Uttar Pradesh) [15]	Cross-sectional study	45	155	22.5	Advanced maternal age, lower socioeconomic status, women residing in a rural area with primary or illiterate education status	-	Preterm birth

Author and year of publication (state)	Study design	No of cases	No of Control	Prevalence (%)	Associated Risk factors	*OR/*ARR with 95% CI	Outcomes
Dayanithi, 2018 (Uttar Pradesh) [12]	Cross-sectional study	103	406	25.6	Joint families, [?]Rs 2999/- monthly income, maternal illiteracy, and housewives	-	Preterm birth
Trivedi et al., 2019 (Gandhinagar, Gujarat) [28]	Cohort study	180	1797	9.0	Periodontal disease, long sleep duration during pregnancy, sex during any trimester	-	Preterm birth

N.B: EP- Extreme preterm; VP- very preterm; MLP- moderate to late preterm; UTI- urinary tract infection; LSCS- Lower segment caesarean section; PROM- Premature rupture of membrane; *OR- Odd ratio; *ARR- Assisted relative risk

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