



## Preterm birth rate and dilemma of preterm labor treatment in Asia<sup>☆</sup>

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### 1. Introduction

Preterm birth (PTB) (before 37 completed weeks of gestation) is one of the most important problems that pose dilemmas for both the obstetrician and neonatologist, as it is the leading cause of perinatal mortality around the world [1]. Infants born preterm also have a high risk for infections and neurodevelopmental problems, and the medical and social expenses required to care for these infants have significantly increased over the past few years. However, despite ongoing research, there has been no significant reduction in the preterm labor and birth rate. This may be a result of inadequate understanding of the etiology and pathophysiology of PTB. Moreover, its treatment involves dilemmas due to the regulations and restrictions on medication use in different countries. Therefore, to understand the differences in treatment between countries, it is important to recognize the current statistics and policies of various countries and their treatment modalities. In this article, we will explore the current situation and treatment modalities of Australia, China, India, Japan, and Korea.

### 2. Reviews

#### 2.1. Australia

The Australian Institute of Health and Welfare's Australia's Mothers and Babies 2015 report (Australian Institute of Health and Welfare 2017. Australia's mothers and babies 2015—in brief. Perinatal statistics series no. 33. Cat no. PER 91. Canberra: AIHW) provides up-to-date information on women who have given birth in Australia and their delivery outcomes and infant characteristics. According to the latest annual report, in 2015, 304,268 women gave birth to 308,887 infants in Australia. Of these, PTBs (defined as birth before less than 37

completed weeks of gestation) were noted in 8.7% of mothers with a mean gestational age of 33.4 weeks. These figures have remained static over the last 10 years. Most stillbirths were preterm (85%) compared with live births with only 8%. Infants born preterm were more likely to be admitted to a special care nursery or neonatal intensive care unit (NICU) (74%) than infants delivered at more than 37 weeks of gestation (25%).

Infants born in multiple births were more likely to be born preterm—around 64% of twins and all other multiples (triplets and higher) were born preterm in 2015. Approximately 14% of infants born to indigenous mothers were preterm, as compared with the 8% rate seen in non-indigenous mothers. Other characteristics associated with increased likelihood of PTB included smoking (13% compared with 8% of infants whose mothers did not smoke), residing in more remote areas (13% in very remote areas compared with 8% in major cities), and younger (under 20 years) and older (40 years and over) age (11% and 12%, respectively were preterm compared with 8% in mothers aged 20–39 years).

In addition to clinical assessment, transvaginal ultrasound of cervical length (TVCL) and fetal fibronectin (fFN) measurement are used to aid in the assessment of PTB risk. Risk reduction measures include progesterone therapy and cervical cerclage. Progesterone therapy can be considered from 16 to 24 weeks of gestation for women with a singleton gestation and prior spontaneous PTB (SPTB) or asymptomatic women with an incidentally diagnosed short cervix. If indicated, a vaginal progesterone suppository is recommended daily until 34 weeks of gestation, rupture of membranes, or birth, whichever occurs first. Cervical cerclage may be indicated for women with history of either one or more prior spontaneous preterm and/or second-trimester loss related to painless cervical dilation and in the absence of labor or abruptio placentae or prior cerclage due to painless cervical dilation in the

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second trimester. If preterm labor ensues or there is imminent risk of PTB, intrapartum antibiotic prophylaxis is recommended for prevention of early onset group B streptococcal (GBS) disease (irrespective of GBS or membrane status).

Tocolysis and steroid administration are the main strategies to manage preterm labor. Antenatal corticosteroids (usually < 34 or 35 weeks) and magnesium sulfate (< 30 weeks) are prescribed if labor is established or birth is imminent. Nifedipine is administered as a tocolytic agent. If contraindications exist, other options include indomethacin and salbutamol.

Steroid administration in > 34 weeks of gestation is controversial due to the recent studies in sheep revealing that steroids can have adverse effects on growth and myelination. Magnesium sulfate is generally used, but there is no consensus on the gestational age cutoff. Some clinicians believe that a cutoff of 32 or even 34 weeks is better for neuroprotection.

Transfer to a center with higher service capability may be necessary. This may present with problems due to tyranny of distance and whether to transfer from remote locations. This is dependent on accurate clinical assessment, which is usually fFN measurement, as these remote areas do not have personnel with expertise (i.e., a credentialed clinician) in cervical length (CL) measurements. Transfer can take a long time and is not appropriate if delivery is imminent. However, services to transfer centrally from remote locations do exist.

PTB is a global health problem that poses dilemmas for both the obstetrician and neonatologist and may be associated with severe complications for the mother and infant. This report describes a case of preterm premature rupture of membranes (PPROMs), chorioamnionitis, and subsequent premature delivery. As the case unfolds, the text provides a useful dialogue to discuss the complexities encountered in managing preterm labor and delivery, including the use of antibiotics in the antenatal and perinatal period, current opinions surrounding GBS prophylaxis, evidence base for drugs to improve neonatal outcome, and optimal mode of delivery.

## 2.2. China

Premature delivery is the primary reason for fetal diseases and deaths. Over 70% of perinatal infant deaths are caused by premature births. Presently, one case of premature infant death occurs every 30 s, and survivors may live with severe complications such as acquired respiratory distress syndrome (ARDS), cerebral palsy, intracranial hemorrhage, and premature retinopathy. In China, premature delivery is defined as the birth of an infant at more than 28 weeks and less than 37 weeks of gestation. The morbidity of premature delivery presents 5–15% of total births and is even up to 5–18% in northern China. As a maternal-fetal medicine (MFM) and perinatal infant rescue center, our hospital found that the morbidity of premature delivery has already reached 15% in the recent 5 years. Premature delivery could place undue burden on both families and the society; however, effective methods of completely preventing PTB have not yet been developed.

The problems are as follows:

1. The specific launch mechanism of spontaneous premature delivery is still unclear. Although many theories have been proposed to explain the sequence of events that culminate in labor and delivery, the exact metabolic and endocrine pathways are yet unknown.
2. There is no measure to predict premature delivery effectively. The tests of CL and fetal fibronectin (fFN) vaginal secretion are now widely used to predict premature delivery. For those who did not deliver in two weeks, the negative result is more valuable than the positive one.

There was also a study showing that a positive fFN is significantly associated with SPTB [2]. A retrospective cohort study of asymptomatic twin pregnancies managed by a single MFM practice from 2005 to 2016

was conducted. One hundred fifty-five patients were included, 129 (83.2%) of whom had a negative fFN and 26 (16.8%) had a positive fFN. Baseline characteristics were similar between groups, except for the CL at the time of diagnosis of short cervix (15 mm in the positive fFN group versus 20 mm in the negative fFN group,  $p = 0.02$ ) In asymptomatic women with twin pregnancies and a shortened CL, a positive fFN is significantly associated with SPTB and can modify the risk substantially. When performing a CL assessment in a twin pregnancy, fFN testing should be done concurrently.

3. PTB is the leading cause of infant morbidity and mortality worldwide, but current interventions to prevent prematurity are largely ineffective. PTB is increasingly recognized as an outcome of a variety of pathological processes. Despite current research efforts, the mechanisms underlying these processes remain poorly understood and are influenced by a range of biological and environmental factors [3]. The preventive methods of premature delivery are limited, especially for twin births.
4. The drug therapeutic effect on PTB to inhibit uterine contraction is limited [4]. There was a health record review of consecutive patients with preterm labor (of the 510 transports reviewed, 488 met all inclusion criteria with the following characteristics: mean age 26.1 years, mean gestational age 31.2 weeks, mean transport time 80 min, 61.0% multiparous, 13.3% twins, mean initial dilatation 1.8 cm) Tocolytics were associated with decreased contraction frequency in more than two-thirds of those treated. However, nearly half of those who did not receive treatment also had decreased contractions, and the effect did not reach statistical significance.

Atosiban causes mild side effects, but it is very expensive, with a cost-effectiveness ratio of 0.67. This makes it unsuitable as first-line medication. Presently, nifedipine is the first-line medication with limited clinical effect. Adrenoceptor agonists and prostaglandin synthase inhibitor have strong side effects. Once premature labor occurs, no drug can effectively inhibit uterine contractions.

5. The long-term prognosis of preterm infants is uncertain. Premature intrauterine infection cannot be completely prevented.

After all, China has a vast territory, and there are differences in not only the morbidity of PTB and perinatal death in the city and countryside, in northern and southern part of China, but also the therapy. The distribution of PTB across China is unbalanced, and neonatal mortality rate associated with PTB is high [5].

## 2.3. India

A recent systematic review in Lancet estimated that India has a preterm birth rate of 13.6% and is amongst one of the top 5 countries for number of preterm births [6]. According to the National Family Health Survey 2015-16 (NFHS-4), a nationwide district-level demographic health survey, the infant mortality rates in India are 41/1000 births [7]. Most of the infant mortality has been reported to be associated with preterm births [8].

However, there are no detailed and accurate reports on the prevalence rates of PTB throughout India [9,10]. Therefore, the Translational Health Science Technology Institute (THSTI), with the support of the Department of Biotechnology, Ministry of Science & Technology, Government of India, initiated a hospital based cohort: GARBH-Ini: interdisciplinary Group for Advanced Research on Birth outcomes – DBT India Initiative. The primary objective of this study is to identify multidimensional correlates of PTB throughout India. Out of the first 1741 completed pregnancies, there were 1659 live births and of these 245 (14.5%) were born preterm [11]. It is important that similar studies are initiated all over India in order to have more accurate PTB rates throughout the different regions. We believe that such studies will help

in formulating national policies to prevent PTB and reduce deaths among premature baby.

Consistency in reporting measures will also lead to more accurate estimates of the rates of preterm birth across India. First trimester dating ultrasound is considered as the best method for assessing the period of gestation. However, in community-based hospitals, first trimester ultrasonography is not always available and thus the date of last menstrual period is used to assess period of gestation. The management for PTL in India revolves primarily around the use of tocolytics, corticosteroids, antibiotics and progesterone therapy. The commonly used tocolytics are Beta-mimetics (isoxsuprine hydrochloride and ritodrine hydrochloride), calcium channel blockers (nifedipine), prostaglandin synthetase inhibitors, magnesium sulfate. Each tocolytic has been studied for its own side effects, and degree of efficacy [12,13].

As reported by WHO, post-delivery the management of the PTB could reduce deaths by 50% by increasing case management of neonatal infections, improved thermal care and feeding support for premature babies, and scaling up Kangaroo Mother Care [14]. Across several Indian states, some hospitals have developed a dedicated newborn care space that has basic equipment and standard protocols to care for newborns. Some hospitals have experimented with the use of alternative teams of ward aides, termed newborn aides, specially trained in newborn care by largely mobilizing internal resources. A two-year follow-up study reported reduction of 14%, neonatal mortality in the first year and by 21% in the second year [15].

In a developing country like India large disparities in health care exist ranging from cities to rural sectors. High incidence of infant mortality and other child health related issues are indicators of this high level inequality in access to healthcare and sanitation in the deprived areas. Other factors that are reported to affect infant mortality rates are lack of nutrition and even basic education [16–19]. The healthcare sector and the government need to come up with remedial programs involving multiphasic schemes. Firstly providing basic education in these areas, especially to girls along with provision of better nutrition may be considered a major step. Furthermore, an overall improvement in quality of life would reduce the risk of preterm birth and its related infant mortality rates. In the later phase, improvement in treatment and better prediction of PTB using new technologies and high-throughput -omic platforms would be required to help lowering the rates of PTBs.

#### 2.4. Japan

The PTB rate of Japan has continued to increase steadily from 1980 to 2000 but remained largely unchanged after that. The latest confirmed vital statistics of the population are those of 2016, and according to that, there were 976,978 live births including 54,594 PTBs (5.6%) [20]. Although Japan has failed to further reduce PTB rate, early neonatal mortality rate maintains a very low value of 0.8% in 2016 [21], and infant and neonatal mortality rates are now among the lowest compared to those in other Organization for Economic Cooperation and Development countries [22]. Even children born at 22–24 weeks of gestation, mortality rate and rate of developing cerebral palsy were as low as 26.1% and 17.4%, respectively [23]. This number is one of the lowest among the countries that are part of the International Network for Evaluation of Outcomes (iNEO) in neonates [24]. However, it is also true that there are many problems still to be solved with respect to prevention and treatment of premature birth in Japan.

The largest detailed databank in Japan is the Perinatal Care Database managed by Perinatology Committee of Japan Society of Obstetrics and Gynecology. This database contains the data of 244,500 births; 25% of the data were covered from the data of the Ministry of Health, Labour and Welfare of 979,818 births. Although this database is the largest databank in Japan, it has few problems. First, as mentioned above, it is not the whole national data but only includes the data of all clinical resident training hospitals and a few voluntary hospitals, just

covering only 25% of all births. In addition, it is not tied to a neonatal or pediatric database and infertility treatment or assisted reproductive technology database, making these data unsatisfactory. Thus, for grasping the current situation of perinatology in Japan, constructing a database that includes detailed information and can link with other databases is urgently desired.

Another problem to be solved with respect to prevention and treatment of PTB is regarding restrictions of medicines that can be used in Japan, which are not present in other countries. Compared with other countries, several medicines and anti-PTB devices are still not included in the insurance coverage in Japan such as progesterone vaginal tablets, oxytocin antagonists, and pessary. 17-Hydroxyprogesterone can be used in Japan; however, the dose is half (125 mg) of that commonly used in other countries. Moreover, there is no strong evidence showing the effectiveness of all these medications and anti-preterm devices in the Japanese population. Hence, the main interventions that can be used in Japan for PTB are still ritodrine and magnesium sulfate. To make things even worse, many obstetricians still blindly use these drugs in the long term. It seems necessary to reform awareness focusing on evidence.

#### 2.5. Korea

PTB is one of the most common complications during pregnancy and primarily accounts for neonatal mortality and morbidity including long-term sequelae such as cerebral palsy and developmental disability.

The survival rate (SR) of very low birth weight infants (VLBWIs) (birth weight < 1,500 g) and extremely low birth weight infants (ELBWIs) (birth weight < 1,000 g) is a health indicator of NICU outcomes. According to the Korean Neonatal Network [25], the SR of VLBWIs significantly increased to 85.7% in the 2010s compared with the 83.0% rate observed in the 2000s. There was also a significant increase in the SR of ELBWIs from 66.1% to 70.7%.

Threatened preterm labor (TPL) is the progression of cervical dilation and ripening caused by regular uterine contractions occurring before 37 weeks of pregnancy, which may result in PTB. To prevent PTB, the most frequently used tocolytic in Korea is ritodrine. The efficacy and safety between magnesium sulfate and ritodrine are similar, and thus, magnesium sulfate can be a substitute tocolytic. According to Hwang's report [26], as first-line tocolytics, beta-agonists (ritodrine) were used most frequently (62%), followed by magnesium sulfate (22%), calcium channel blockers (11%), and atosiban (4.6%). In approximately 44% of women who used first-line tocolytics, second-line tocolytics were required. However, the recommendation restricting the use of ritodrine for 48 h and the Korean medical insurance policy only allowing three prescriptions of atosiban between 24 and 34 weeks of gestation raise a clinical dilemma.

The most effective treatment of PTB is prediction and prevention of its risks. Risk factors of PTB include history of PTB, short CL, multiple pregnancies, ethnicity, smoking, uterine anomaly, and history of curettage or cervical conization. Among these risk factors, history of PTB and short CL are the most important predictive factors [27]. Progesterone supplement therapy is one of the few proven effective methods to prevent PTB in women with history of spontaneous PTB and those with short CL. There are 2 types of progesterone therapies used for the prevention of PTB: weekly intramuscular (IM) injection of 17-alpha hydroxyprogesterone caproate (17 $\alpha$ -OHPC) and daily administration of natural micronized progesterone vaginal gel, vaginal suppository, or oral capsule. However, the efficacy of progesterone therapy to prevent PTB may vary depending on the administration route, form, dose, and indications for treatment. Currently, the Preterm Birth Committee of Korean Society of Maternal Fetal Medicine is conducting "A multi-center, randomized, open-label, investigator-initiated trial of vaginal compared with intramuscular progesterone for prevention of PTB in high-risk pregnant women: VICTORIA study." In this trial, 360 pregnant women with history of PTB and/or short CL will be recruited from 24

medical centers nationwide. The study will compare the efficacy and safety of 2 regimens of progesterone supplement therapy — weekly IM injection of 250 mg of 17 $\alpha$ -OHPC and daily vaginal administration of 200 mg of micronized progesterone. In Korea, most clinicians use vaginal micronized progesterone suppository or 17 $\alpha$ -OHPC IM injection for pregnant women with short CL and PTB history [27].

The PTB registry, named Korean Preterm Collaborate Network (KOPEN), was established in Korea in 2016. The purpose of KOPEN was to identify the risk factors of PTB and status of treatment through the registry of domestic multicenter registry and lay the foundations for the evidence-based prevention and development of management indicators for PTB. Obstetricians and researchers from 20 institutions nationwide participated in the study. KOPEN collected demographic, clinical, and delivery data of pregnant women who were diagnosed with preterm labor, Incompetent internal os of cervix (IIOC), or PPROM between 15 and 34 weeks of gestation.

A total of 861 pregnant women were included in the study, of which 683 had delivery data. This research has helped to elucidate the demographic and clinical factors associated with PTB. Based on this research, pre-pregnancy counselling may be recommended for women at risk of PTB when considering pregnancy. In addition, continuing medical research on PTB is underway, and the results of the study will be published in the future.

In the cases of PPROM, antibiotics have been administered to prevent intra-amniotic inflammation. From 1993 to 2003, ampicillin and/or cephalosporins or their combination was used (regimen 1). A new regimen (ceftriaxone, clarithromycin, and metronidazole) was used from 2003 to 2012 (regimen 2). The administration of ceftriaxone, clarithromycin, and metronidazole was associated with a more successful eradication of intra-amniotic inflammation and prevented secondary intra-amniotic inflammation more frequently than the antibiotic regimen, which included ampicillin and/or cephalosporins, in patients with PPROM [28].

The PTB rate in Korea has decreased for decades but still remains high and is the cause of the increased use of health-care resources and societal costs, with devastating social implications for survivors and their families. Further research is needed on the causes of PTB and the effectiveness of interventions. Ultimately, success of a population's health strategy to reduce the PTB rate will be measured by a decreased rate of prematurity in the entire population. A concerted national effort is needed to scale up evidence-based strategies and drive research to improve outcomes for all preterm infants.

### 3. Conclusion

In this article, we explored and collected the statistical data on PTB rates and the treatments used for preterm labor in five countries. The PTB rates between countries were similar, and the infant morbidity and mortality rates have not declined over the past years. This is due to the limited range of medications available and uncertainty in methods for predicting preterm labor. As mentioned in the introduction, we have yet to gain an adequate understanding of the etiology and pathophysiology of PTB. Therefore, to reduce PTB rate and improve its outcome, further investigation and research are needed. To facilitate this process, global awareness and active involvement in the issue are more essential than ever before.

### Conflicts of interest

We, the authors, do not have any conflicts of interest related to this manuscript.

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