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TOCOLYTIC AND NEUROPROTECTION IN PRETERM LABOR

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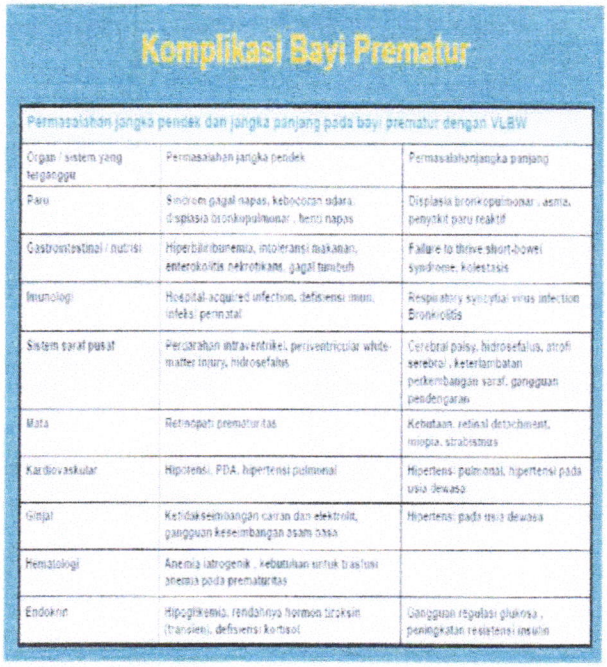
Preterm birth (PTB) is any delivery, regardless of birth weight, that occurs before 37 completed weeks from the first day of the last menstrual period. Preterm delivery is the leading cause of the perinatal morbidity and mortality worldwide. Almost 13 million babies every year worldwide are born preterm. An estimated 28 % of the 4 million annual neonatal deaths worldwide are directly attributable to preterm birth . Over a million babies every year die of prematurity. So, every minute 2 babies die of preterm birth . Accounts for 75% of perinatal mortality and make up more than 50% of long-term morbidity associated with poor perinatal outcomes . Over 85 % occur in Asia and Africa. The highest rates in Africa and North America (11,9% and 10.6%).



The incidence of disability and neurodevelopmental problems among survivals remains high and problematic . Major disabilities (moderate-severe mental retardation, sensorineural hearing loss/blindness cerebral palsy, and epilepsy) present in up to 25% of VLBW.

Neurodevelopmental dysfunctions (learning disabilities, low average IQ scores, ADHD, neuropsychological deficits, visual motor integration, temperament difficulties, language delays,

emotional problems and regulatory disorders) present in 50–70% of VLBW. Those deficits can be seen in premature infant with IVH/PVL or without any ultrasound abnormality.

Cost of Preterm Birth ; Medical care services: 16.9 billion ($ 33,200 per preterm infant) - 2/3 total cost. Maternal delivery cost: 1.9 billion ($ 3,800 per preterm infant). Special education services: 1.1 billion ($ 2,200 per preterm infant). Lost household and labor market productivity: 5.7 billion ($11,200 per preterm infant) . The annual cost of PTB in US exceeds $ 5 billion and the rate of PTB has increased in recent years . Treatment should be initiated only once the diagnosis is made The diagnosis of spontaneous preterm labor (PTL) and accurate prediction of PTB is notoriously difficult. PTL is a clinical diagnosis. Regular contractions with cervical effacement or dilatation are required for diagnosing established labor. The clinical diagnosis of PTL ; Contractions that are painful, palpable, last longer than 30 seconds and occur at least 4 times per 20 minutes .Evidence of a change in the position, consistency, lenght and/or dilatation of the cervix. Contractions occur at a frequency of 4 times per 20 minutes or 8 per 60 minutes Accompanied by one of the following : PROM, Cervical dilatation > 2 cm, Effacement > 50%, Change in cervical dilatation or effacement detected by serial examinations. The clinical diagnosis of PTL; Contractions ≥ 6 /hour. Cervical dilatation ≥ 3 /cm *and or* effacement ≥ 80%. Vaginal bleeding. Documented change in the cervical exam . Standard techniques of clinical diagnosis may not accurately detect PTL, either missing the diagnosis or prompting unnecessary hospitalization and treatment. Patients may not perceive contractions and that contractions are at times difficult to differentiate from benign Braxton-Hicks contractions of normal pregnancy. Digital assessment of the cervix lacks reproducibility when the dilatation is < 3 cm or effacement is < 80%. Clinical evaluation alone can easly suggest prematurity when it is absent and miss it when it is presen.

Clinical and Biochemical Markers : A number of studies have attemped to identify clinical and biochemical markers. Source of biologic fluid : Serum or plasma. Amniotic fluid, Urine, Vagina and cervical secretions, Saliva, Periodontal fluid .

Ability of Clinical Markers to Predict Preterm Labor*

Marker	*Test*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*
Risk scoring systems	Risk factors[1-3]	88 to 92	28 to 30	94 to 98	41 to 76
Assessment of cervical length	Manual examination[10,16,17]	8 to 64	68 to 96	7 to 32	89 to 94
	Ultrasound examination[11,12]	76 to 100	55 to 59	55-75	93 to 100
Monitoring of uterine activity	Patient-perceived[12]	NS	NS	NS	NS
	Tocodynamometry[14,15,17]	18 to 58	45 to 94	7 to 20	82 to 94
Vaginal bleeding	Pelvic examination[15,17]	8 to 36	89 to 95	21 to 82	82 to 97

Table II Markers of intrauterine infection in pregnant women in labor

Infection site	Marker
Amniotic fluid	Bacteria
	Low glucose level
	High white blood cell count
	High G-CSF
	High IL-1 level
	High IL-6 level
Cervix or vagina	Bacterial vaginosis
	High G-CSF
	High tumor necrosis factor-α level
	High IL-1 level
	High IL-6 level
	High IL-8 level
	High fetal fibronectin level
Serum	High G-CSF
	High IL-6 level
	High tumor necrosis factor-α level
	High C-reactive protein level

Cervical Length (TVU CL) ; Examination of the cervix with ultrasound is superior to vaginal examination. The shorter the cervix, the higher the risk for PTB and vice versa. Ultrasound assessment of the cervix in normal pregnancy shows that cervical effacement starts around 32 weeks. In pregnancies affected by PTL the process may begin between 16 and 24 weeks. Effacement begins at the internal os and can be visualized as cervical shortening and funneling, a process that occurs before dilatation of the external os. Lesser cervical length means greater risk.

Likelihood of PTB is inversely proportional to cervical length measured at 18-28 weeks. A lenght of $\leq$ 2.5 cm is the treshold for abnormal condition.

Fetal Fibronectin (FFN), An extracellular glycoprotein described as the glue that attaches the fetal membrane to the underlying uterine decidua. Is normally absent in cervicovaginal secretions between weeks 22 and 37 of pregnancy. Its presence ($\geq$ 50 ng/mL) between 22 to 24 weeks is a predictor of spontaneous PTB. Its absence makes PTB unlikely. Diagnosis Diagnosis (Modern); Persistent uterine contractions($\geq$ 6 /hour) *and* TVU CL $\leq$ 20 mm *or*TVU CL 20-30 mm and FFN (+) .

Efforts to prevent PTB can be disappointing. Obstetrics care must focus on strategies to improve the outcome of preterm infants. 30% spontaneously resolves, < 10% give birth within 7 days, 50% hospitalized women give birth at term.

Preventive programs or interventions goals: (1) Decrease of uterine contractions to delay preterm delivery , (2) Optimize the fetus for life extra-uterine .(3) Transfer the mother to a tertiary referral hospital where a neonatal intensive care unit is available. Primary effort , before or

during pregnancy to prevent & reduce risk . Secondary effort, eliminating or reducing risk in women with known risk factors . Tertiary effort, initiated after the process parturition begun with a goal preventing delivery or improving out comes for preterm infants . Maternal risk factors for preterm birth ;

Covariate	Contrast	Odds ratio estimate	Lower 95% confidence limit for odds ratio	Upper 95% confidence limit for odds ratio	p-Value
Age (cat)	2. Age > 35 vs. 1. Age < 35	1.234	0.699	2.177	0.4686
BMI	2. BMI > 25 vs. 1. BMI < 25	1.962	1.033	2.676	0.0365
Employment	1. Physical work vs. 2. Intellectual work	1.947	1.182	3.207	0.0089
Diabetes mellitus	1. Yes vs. 2. No	2.236	0.942	5.548	0.0675
Chronic arterial hypertension	1. Yes vs. 2. No	2.621	0.746	9.208	0.1327
Asthma	1. Yes vs. 2. No	1.535	0.367	6.580	0.5489
Endocrinological diseases	1. Yes vs. 2. No	1.420	0.594	3.398	0.4307
Congenital/acquired uterine malformations	1. Yes vs. 2. No	2.660	0.602	11.748	0.1967
Previous abortion	1. Yes vs. 2. No	1.954	1.162	3.285	0.0116
Previous PTBs	1. Yes vs. 2. No	3.402	1.342	8.626	0.0099
Previous cesarean section	1. Yes vs. 2. No	2.904	1.066	7.910	0.0371
Previous pregnancies < 1 year before current delivery	1. Yes vs. 2. No	0.919	0.398	2.124	0.8440
IVF	1. Yes vs. 2. No	2.065	0.263	16.222	0.4906
Cigarette smoking	1. Yes vs. 2. No	1.340	0.702	2.557	0.3746
Amniocentesis/villocentesis	1. Yes vs. 2. No	1.006	0.540	1.875	0.9845

G.C. Di Renzo et al. / European Journal of Obstetrics & Gynecology and Reproductive Biology 159 (2011) 342–346

Tocolytic; Single or Multiple ?

Corticosteroid: Single - Multiple .Tocolytics : Acute and Maintenance, First Choice and Second Choice. Tocolytics ; Abolish contractions temporarily,Doesn't remove underlying stimulus, Delay delivery by hours to days. Indication; Women with preterm labor at a gestational age at which a delay in delivery will provide benefit to the newborn. Because tocolytic therapy generally is effective for up to 48 hours, only women with fetuses that would benefit from a 48-hour delay in delivery should receive tocolytic treatment.

Treatment goals; delay delivery by at least 48 hours so that corticosteroids given to the mother can achieve their maximum fetal/neonatal effect. (Predelivery administration of betamethasone reduces the risk of neonatal death, RDS, IVH, and NEC in premature neonates). Provide time for safe transport_of the mother, if indicated, to a facility that has an appropriate level of neonatal care. Prolong pregnancy when there are underlying, self-limited conditions that can cause labor, such as pyelonephritis or abdominal surgery (appendectomy).

Gestational age limits; Lower limit , tocolytics are generally not indicated prior to neonatal viability since these drugs do not delay delivery for more than a few days. Except to inhibit contractions after a self-limited event that has been associated with preterm labor, such as Acute Pyelonephritis or appendicitis with appendectomy. Upper limit , Thirty-four weeks of gestation. Contraindications ; Women with preterm contractions without cervical change, Cervival dilation > 3 cm, The maternal/fetal risks of prolonging pregnancy or the risks associated with these drugs are greater than the risks associated with preterm birth. Established contraindications to labor inhibition include : Intrauterine fetal demise, Lethal fetal anomaly, Nonreassuring fetal status, Severe preeclampsia or eclampsia, Maternal hemorrhage with hemodynamic instability, Intraamniotic infection, Maternal contraindications to the tocolytic drug.

The selection of an appropriate labor-inhibiting agent should be based upon efficacy and safety. The drug should be safe for the mother, fetus, and neonate. If the first tocolytic does not successfully inhibit contractions, discontinue it and begin therapy with a second agent. Concurrent use of more than one tocolytic agent should be undertaken with caution because of the increased risk of side effects. There are no data on the role of repeated courses of tocolytics for treatment of recurrent preterm labor. In patients receiving antenatal corticosteroids, discontinue tocolytics 48 hours after administration of the first corticosteroid dose.

Options; Cyclooxygenase inhibitors and calcium channel blockers had the highest probability of delaying delivery and improving neonatal and maternal outcomes. For women 24 to 32 weeks of gestation who are candidates for tocolysis, use indomethacin as first-line therapy for labor inhibition. For women 32 to 34 weeks of gestation, use nifedipine for initial treatment of preterm labor, due to adverse fetal effects of indomethacin use at this gestational age .

Indomethacin Side Effect; Maternal: Nausea, gastritis, and emesis (4%), Platelet dysfunction may occur. Alterations in maternal cardiovascular physiology are minimal (eg, myocardial infarction, stroke). Fetal : Constriction of the ductus arteriosus , Oligohydramnios.

Ca channel Blocker; Meta-analysis of 13 randomized trials (1000 patients) specifically comparing nifedipine versus beta-adrenergic receptor agonists: Nifedipine had fewer deliveries within 7 days (RR 0.82, 95% CI 0.70-0.97; 37 versus 45 percent) and before 34 weeks of gestation (RR 0.77, 95% CI 0.66-0.91; 48 versus 62 percent), but there was no significant difference in delivery within 48 hours of treatment (RR 0.84, 95% CI 0.68-1.05; 21 versus 24 percent) Nifedipine was also associated Significant reductions in RDS, NEC, IVH, neonatal jaundice, admission to the neonatal intensive care unit, and Had a better side effect profile.

Dose; Initial loading dose of 20 mg orally, followed by 20 mg orally in 90 minutes. If contractions persist, 20 mg can be given orally every 3 to 8 hours for up to 72 hours, with a maximum dose of 180 mg/day. ACOG suggests a 30 mg loading dose and then 10 to 20 mg every four to six hours . Maintenance : There are several theoretical rationales for considering maintenance tocolysis after successful arrest of the initial episode of PTL: 1. the underlying

stimulus for labor may persist and cause a recurrence. 2. the myometrium, having experienced a recent episode of PTL, may be in a chemical state of preparedness and thus have a low threshold for recurrence Maintenance tocolytic therapy is ineffective : If a second episode of acute preterm labor occurs, the indications for retreatment are the same as for a primary episode.

Beta-agonists ; A Cochrane review, which included 11 randomized trials comparing oral beta-mimetics with alternative therapies or placebo for maintenance therapy after threatened PTL, concluded there was no significant benefit to oral beta-mimetic therapy. Outcomes evaluated included rate of NICU admission, preterm birth, perinatal mortality, and perinatal morbidity. FDA concluded that the risk of serious adverse events from prolonged terbutaline therapy of preterm labor (beyond 48 to 72 hours) outweighs any potential benefit. The safety of this therapy was unclear. Risks ; An FDA-conducted search of its Adverse Event Reporting System (AERS) identified reports of 16 maternal deaths associated with terbutaline between 1976 and 2009. Between 1998 and July 2009, 12 cases of serious maternal cardiovascular.

MgSO4; A more recent report evaluating 19 RCT reveals that MgSO4 fails to reduce delivery rate within 48 hours.

Recpmmendations ; 1. Administrate tocolytics to selected women with preterm labor. 2.The goal of treatment is to delay delivery so that glucocorticoids can be administered and achieve their maximal effect; allow safe transport of the mother, or to prolong pregnancy when there are underlying, self-limited causes of labor. 3.Treatment can be discontinued after these goals have been achieved. 4. The selection of an agent should be based upon efficacy and safety. 5. If the first tocolytic agent chosen does not successfully inhibit preterm labor, discontinuing it and begin therapy with a second agent. 6. Avoid routinely administering multiple tocolytics in patients who fail therapy with a single agent. 7. Not using maintenance tocolysis .

Fetal Neuroprotection .

Preterm birth and low birth weight are important public health problems, have a higher risk of a developing neurological problems such as cerebral palsy (CP) and impairment of cognitive function. The risks increases , with decreasing GA at birth. Preterm infants born with PE had a lower incidence of adverse CNS outcomes than without PE. The use of MgSO4 for PE may underlie the potential association between administration of MgSO4 and CP. MgSO4 given before anticipated early preterm birth reduces the risk of CP in surviving infants. The exact mechanism is still unknown, Two theories that describe how magnesium may inhibit neuronal damage : Hypoxic-ischaemic damage and Inflamatory damage .

Hypoxic-ischaemic damage : CP is though to be a result of periventricular white matter damage that predominates, <32 weeks gestation. Hypoxic-ischaemic damage is a result of low oxygen and glucose supply; leads to excessive glutamate release , Glutamate stimulates the N-

methyl-D-aspartate (NMDA) ; MgSO4 is an NMDA receptor antagonist and have proven to be strong neuroprotectants in various animal models.

Inflamatory damage ; There is a strong correlation between spontaneous preterm birth and intrauterine inflamation. Fetal brains subjected to inflamation that were treated with MgSO4 did not display neuronal injury associated with fewer dendritic processes. MgSO4 therapy given to women at risk of preterm birth substantially reduced the risk of CP in their infants (RR 0.68, 95% CI 0.54-0.87).

Indication ; Imminent preterm birth (from viability to ≤ 31 + 6 weeks) is : Active labour with ≥ 4 cm of cervical dilatation +/- PPROM , Planned preterm birth for fetal or maternal indications , Singleton and multiple pregnancies,Nulliparous and parous , Anticipated vaginal or Caesarean delivery , Any reason for anticipated preterm birth . Exclusion criteria ; MgSO4 already administered for preeclampsia- eclampsia , < 12 hours since discontinuation of previous MgSO4 infusion , MgSO4 contraindicated . Dosage ; Loading dose 6 g IV over 20-30 minutes. A maintenance infusion of 2 g / hr for 12 hours or until delivery, whichever comes first.