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Predicting Severe Neonatal Jaundice from Maternal Risk Factors

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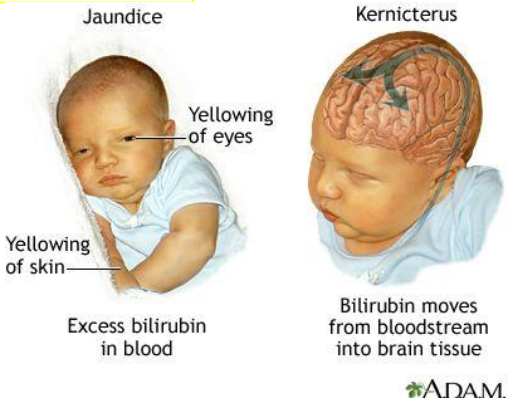
Kulliyyah of Medicine

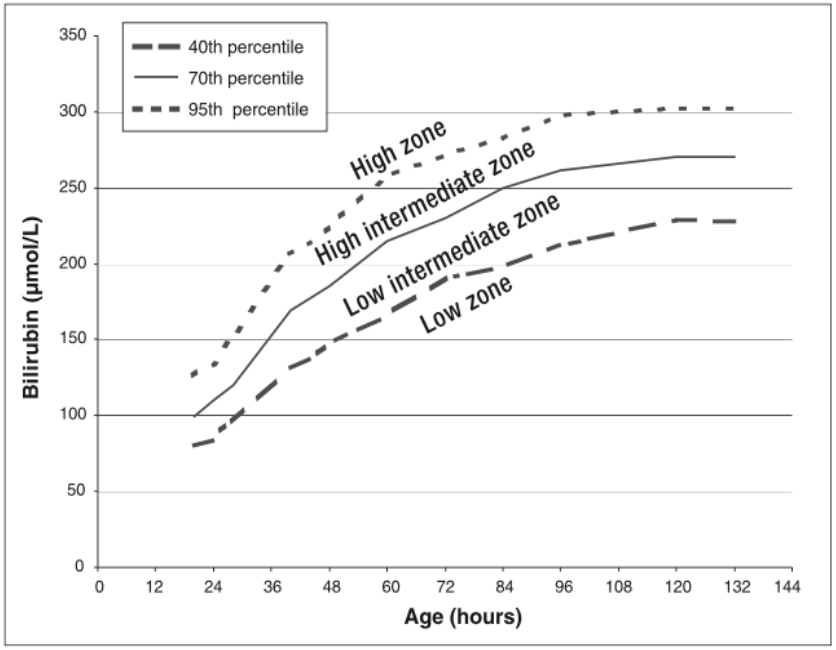
Predicting Severe Neonatal Jaundice from Maternal Risk Factors

- Severe Neonatal Jaundice
- World Wide Burden
- Risk factors for Severe NNJ
- Prediction of Severe NNJ
- Predicting with current Obstetrics Scenarios
- ? Individualised / Customised Risk Assessment?

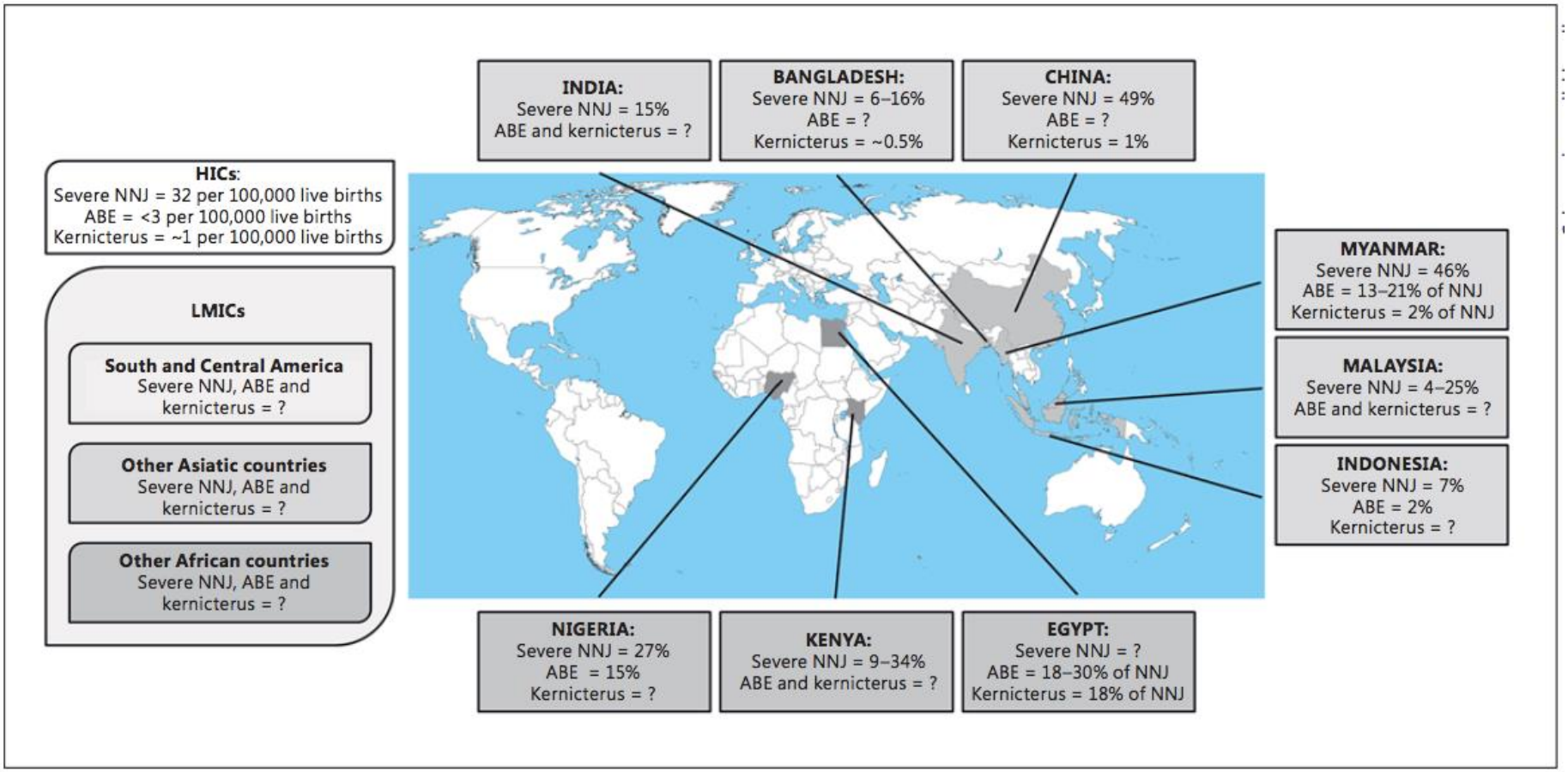
Neonatal Jaundice

- ✧ NNJ common clinical condition in newborns
- ✧ Severe Neonatal Jaundice
  - 8% - 11 %
  - TSB above 95p for age during the first week of life (343 µmol/L)
- ✧ Levels rise to high-risk zone
  - → long-term consequences
  - Bilirubin-induced encephalopathy
  - Kernicterus
- ✧ Phototherapy and exchange transfusio
- ✧ Kernicterus continues to be reported worldwide especially in developing countries





Incidence of Severe Neonatal Jaundice



Term Newborn

60% jaundice
2% TSB > 340 µmol / L
ABE very rare, unless > 425 µmol / L
Kernicterus (2/3 > 425 µmol / L)

Total Serum Bilirubin (TSB)

Healthy term babies – level unknown
Lower TSB levels in presence of risk factors

35-36 weeks : major risk factors for severe NNJ

BMJ Paediatrics Open

Burden of severe neonatal jaundice: a systematic review and meta-analysis

Tina M Slusher,[1,2] Tara G Zamora,[1] Duke Appiah,[3] Judith U Stanke,[4] Mark A Strand,[5] Burton W Lee,[6] Shane B Richardson,[7] Elizabeth M Keating,[8] Ashajoythi M Siddappa,[1,2] Bolajoko O Olusanya[9]

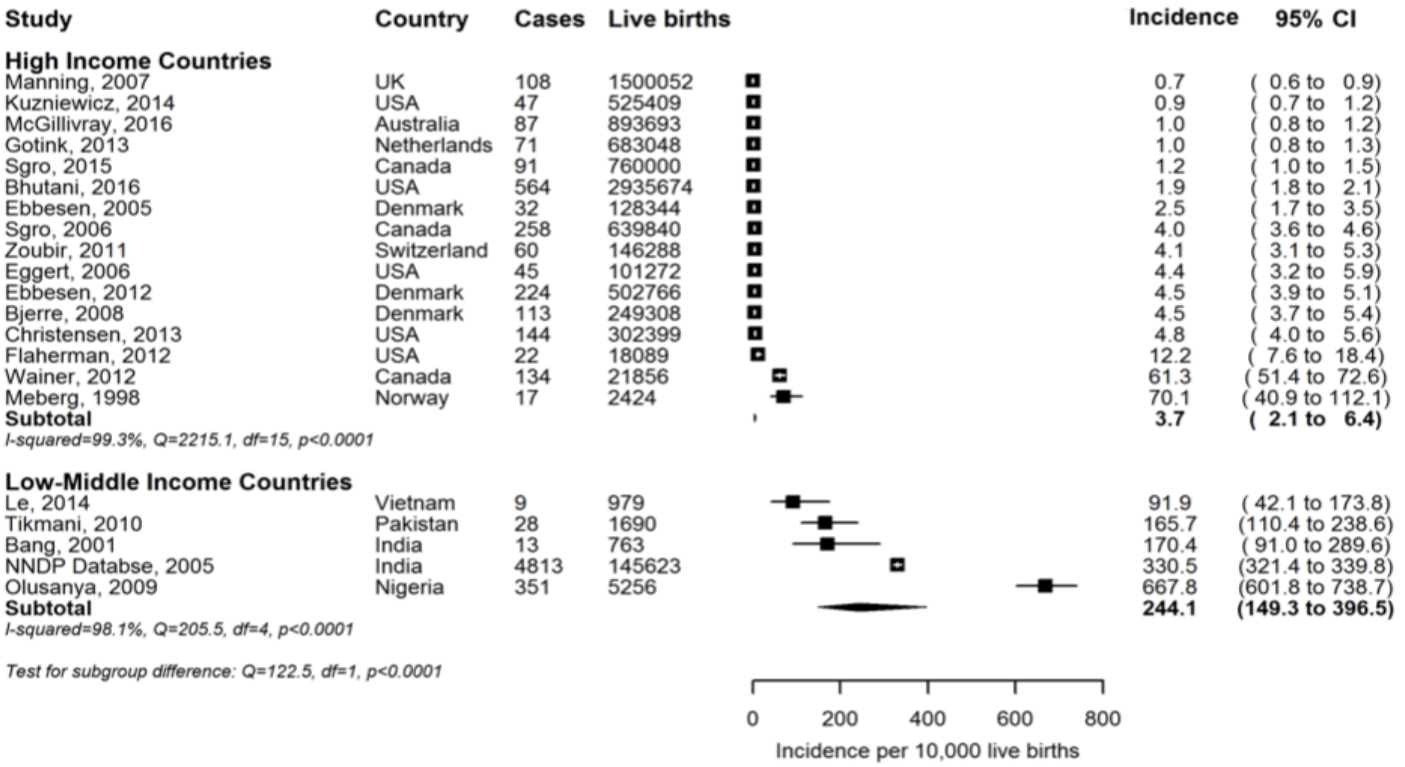


Figure 2 Pooled incidence (per 10 000) of severe neonatal jaundice among all neonates aged 24 months or less according to study quality.

Jaundice related death in infants with significant jaundice

2.8 % (UK)

30.8 % (India)

Slusher BMJ 2019

Table 2 Incidence (per 10 000 live births) of severe neonatal jaundice among all neonates aged 24 months or less by gestation and study design

Characteristics	N	Live births	Incidence	95% CI
Gestation*				
All	9	2 642 234	37.8	6.9 to 205.4
Term and near term	10	5 522 699	4.0	1.9 to 8.8
Term only	2	1 399 840	2.2	0.7 to 7.2
Design†				
Prospective	13	5 426 387	9.7	1.7 to 53.8
Retrospective	8	4 138 386	10.3	1.3 to 80.4

*Test for subgroup differences (Cochran's Q=7.42, p=0.025).
†Test for subgroup differences (Cochran's Q=0.002, p=0.963).
N, no of studies.

Table 3 Incidence of severe neonatal jaundice per 10 000 live births, among all neonates aged 24 months or less

WHO region	N	Live births	Incidence*	95% CI
Overall†	21	9 564 773	9.9	2.8 to 35.6
African	1	5256	667.8	603.4 to 738.5
Americas	8	5 304 539	4.4	1.8 to 10.5
Eastern Mediterranean	1	1690	165.7	114.6 to 238.9
European	7	3 212 230	3.7	1.7 to 8.0
Southeast Asian	2	146 386	251.3	132.0 to 473.2
Western Pacific	2	894 672	9.4	0.1 to 755.9

*Test for subgroup differences (Cochran's Q=346.9, p<0.001).
†I^2=99%, Cochran's Q=34 721, p<0.001.
N, no of studies

Table 4 Incidence of exchange transfusions, per 10 000 live births, among all neonates aged 24 months or less

WHO region	N	Live births	Incidence*	95% CI
Overall†	16	9 437 479	8.4	2.7 to 25.7
African	1	5256	186.5	153.2 to 226.8
Americas	6	5 181 411	0.38	0.21 to 0.67
Eastern Mediterranean	1	1690	17.8	5.7 to 54.9
European	6	3 209 806	0.35	0.20 to 0.60
Southeast Asian	1	145 623	107.1	102.0 to 112.5
Western Pacific	1	893 693	0.19	0.12 to 0.31

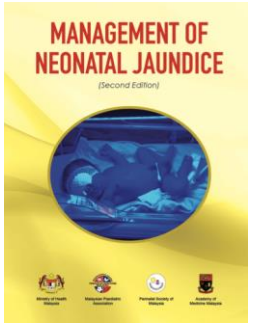
*Test for subgroup differences (Cochran's Q=1501.2, p<0.001).
†I^2=99%, Cochran's Q=8730.7, p<0.001.
N, no of studies.

Slusher BMJ 2019

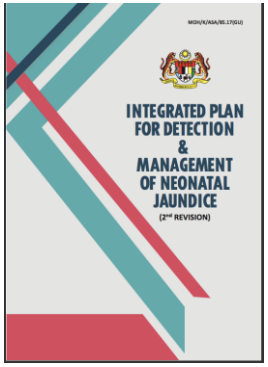
Risk factors for Severe NNJ

Risk factors of severe NNJ are:-

- prematurity
- low birth weight
- jaundice in the first 24 hours of life
- mother with Blood Group O or Rhesus Negative
- G6PD deficiency
- rapid rise of total serum bilirubin
- sepsis
- lactation failure in exclusive breastfeeding
- high predischarge bilirubin level
- cephalhaematoma or bruises
- babies of diabetic mothers
- family history of severe NNJ in siblings



2013



2018

2004

The following are the key elements of the recommendations provided by this guideline. Clinicians should:

1. Promote and support successful breastfeeding.
2. Establish nursery protocols for the identification and evaluation of hyperbilirubinemia.
3. Measure the total serum bilirubin (TSB) or transcutaneous bilirubin (TcB) level on infants jaundiced in the first 24 hours.
4. Recognize that visual estimation of the degree of jaundice can lead to errors, particularly in darkly pigmented infants.
5. Interpret all bilirubin levels according to the infant's age in hours.
6. Recognize that infants at less than 38 weeks' gestation, particularly those who are breastfed, are at higher risk of developing hyperbilirubinemia and require closer surveillance and monitoring.
7. Perform a systematic assessment on all infants before discharge for the risk of severe hyperbilirubinemia.
8. Provide parents with written and verbal information about newborn jaundice.
9. Provide appropriate follow-up based on the time of discharge and the risk assessment.
10. Treat newborns, when indicated, with phototherapy or exchange transfusion.

Prediction of Diseases

- Prediction of aneuploidy / Preeclampsia
  - History + Serum Markers + Ultrasound Markers

- Prediction of aneuploidy
  - Maternal age : **30 %**
  - Maternal age + 2nd tm (serum) + 2nd tm (ultrasound) : **75 %**
  - Maternal age + 1st tm (serum) + 1st tm (ultrasound) : **95 %**

- **History → x % detection rate**
  - **Obstetrics risk (Gp O + Rhesus negative + Diabetes + Siblings SNNJ + antibody)**
  - **Neonatal risk (GA + BW + G6PD + Lactation failure + cephalhaematoma + jaundice within 24 hrs**
- **History + TSB → y % detection rate**
- **History + TSB + ? Genetic → z % detection rate**

Prediction Methods of Severe NNJ

Timed TSB Measurements

Blood Group and Coombs testing

- Group O mother
- ABO isoimmunisation mother
- ABO-incompatible infants positive direct Coombs test → increased need of phototherapy

Glucose-6-phosphate dehydrogenase deficient

End-tidal carbon monoxide

- Prediction not improved by exhaled carbon monoxide in addition to timed TSB

Umbilical cord blood TSB

- PPV and specificity – poor

Universal Haemoglobin Assessment umbilical cord

- does not aid in prediction of severe hyperbilirubinemia

Timed TSB Measurements

- Analysed in the context of the infant's gestational age
- < 38 weeks TSB > p75th – 10 % risk
- 39-40 weeks TSB > p95 – 10 % (evidence level 2b)

- Late preterm (≥ 35 weeks)
  - between 18 h – Day 3
  - p95 -300 µmol / L after 96 h
  - P75 – 12.9 %
  - p40 – p75 – 2.2%
  - p40 – no cases

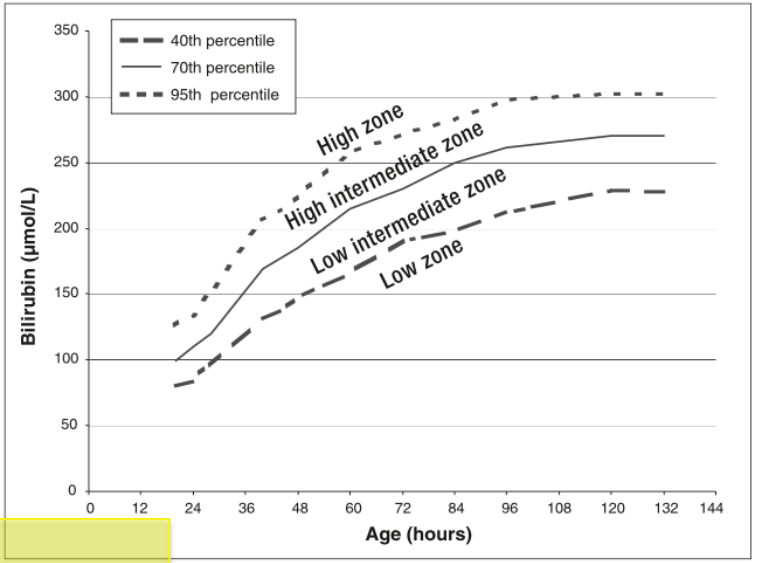


Figure 1) *Nomogram for evaluation of screening total serum bilirubin (TSB) concentration in term and later preterm infants, according to the TSB concentration obtained at a known postnatal age in hours. Plot the TSB on this figure, then refer to Table 4 for action to be taken*

Best available method

Predicting Nonhemolytic Neonatal Hyperbilirubinemia

Mikael Norman, MD, PhD[a,b], Katarina Åberg, RN, RM[c], Karin Holmsten, RN, RM[d], Vania Weibel, RN, RM[e], Cecilia Ekéus, RN, RM, PhD[c]

1999-2012 population-based study Swedish Medical Birth Register, 1 261 948 singleton term infants.
Exclude hemolytic diseases : 23 711 (1.88 %)

Non-overweight, non-Asian mother

Primipara

Mode of delivery	Gestational age, weeks 37	38	39	40	41	>41
VE	16	10	6	4	3	2
Vaginal	7	4	2	2	1.4	1.4
Emergency CS	5	3	2	1.3	1.1	1.0
Planned CS	3	1.0	0.9	2	0.2	1.1

Multipara

Mode of delivery	Gestational age, weeks 37	38	39	40	41	>41
VE	13	7	4	3	1.4	1.4
Vaginal	4	2	1.0	0.8	0.7	0.8
Emergency CS	3	2	1.1	1.0	1.1	0.9
Planned CS	2	1.2	0.7	0.6	0.3	0.5

Individualized risk prediction in developed health care systems
In limited or no resources for blood type / bilirubin screening programs

Mode of delivery	Gestational age, weeks 37	38	39	40	41	>41
Vaginal	8	4	2	1.5	1.2	1.2
Emergency CS	5	3	2	2	1.4	1.3
Planned CS	3	2	0.8	2	1.0	1.2

Mode of delivery	Gestational age, weeks 37	38	39	40	41	>41
Vaginal	12	6	3	2	1.2	0.7
Emergency CS	6	4	2	2	1.0	2
Planned CS	5	2	1.2	0.7	0.0	0.0

Asian mother

Mode of delivery	Gestational age, weeks 37	38	39	40	41	>41
VE	22	14	8	7	8	7
Vaginal	8	5	4	3	3	2
Emergency CS	6	3	4	3	2	1.2
Planned CS	3	1.0	0.6	1.0	2	3

SGA-infants

Mode of delivery	Gestational age, weeks 37	38	39	40	41	>41
VE	16	12	7	5	5	5
Vaginal	8	5	3	2	2	2
Emergency CS	7	6	4	4	2	2
Planned CS	5	3	4	6	1.0	4

ADJUSTED ODDS RATIO (aOR)

GA	: 2.83
Failed VE	: 2.79
VE	: 2.22
Asian mother	: 2.09
Primipara	: 2.06
LGA	: 1.84
Obese mother	: 1.83
SGA	: 1.66
Planned CS	: 0.45

Without ALL
0.7 %

Combination load
0.2 % - 25 %
Highest : GA 37, failed VE + em CS
Lowest : GA41 + planned CS

PEDIATRICS 2015

Individualised risk assessment tool for clinical use

- Collection of a few easily available maternal and obstetric risk factors predicts > 100-fold variation in the incidence of neonatal hyperbilirubinemia
- Enable individualised risk prediction with interactions between different risk factors taken into account

Trend of Gestational Age at Delivery

Delivery at reducing GA

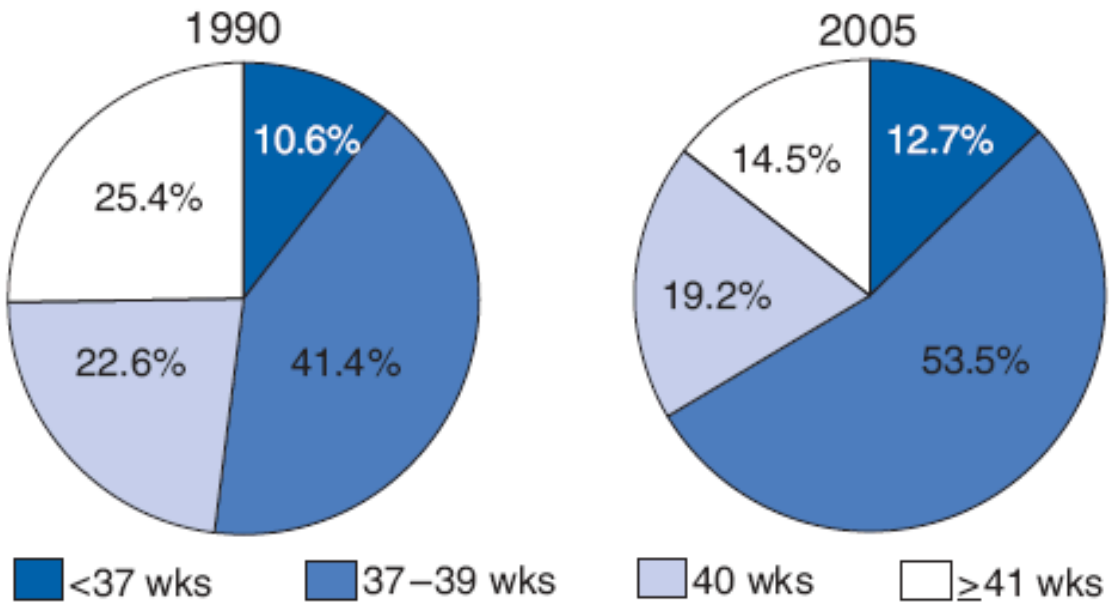
New Gestational Age Designations

Early Term	Full Term	Late Term	Post Term
37 weeks - 38 weeks & 6 days	39 weeks - 40 weeks & 6 days	41 weeks - 41 weeks & 6 days	42 weeks and beyond

37 38 39 40 41 42 43

Old Gestational Age Desig

"Term" birth
Gestation between 37 weeks and 42



Induce beyond 42 weeks?

New Gestational Age Designations

Early Term	Full Term	Late Term	Post Term
37 weeks - 38 weeks & 6 days	39 weeks - 40 weeks & 6 days	41 weeks - 41 weeks & 6 days	42 weeks and beyond

- Favourable perinatal outcomes between 40 and 42 weeks
- The risk of adverse perinatal outcome increases gradually after 40 weeks
- Induction of labour from 41 weeks onwards improves perinatal outcome → confirmed by meta-analysis
- Induction at 41 weeks – accepted policy in many country
- RCOG/ NICE → women should be offered between 41 – 42 weeks

- Extended to or beyond 42 weeks or 294 days or more
- Increased perinatal morbidity and mortality
- WHO recommends after 42 weeks

Induction at 41 weeks vs Expectant till 42 weeks

- Fewer Perinatal Death 2 vs 16
  - RR 0.33, 95% CI 0.14 to 0.78
- Fewer Stillbirth 1 vs 10
  - - RR 0.33, 95% CI 0.11 to 0.96
- Fewer Caesarean
  - RR 0.92. 95 % CI 0.85 to 0.99
- Marginal increase in operative vaginal birth
  - RR 1.07, 95 % CI 0.99 to 1.16
- No evidence of difference
  - Perineal trauma
  - Post partum haemorrhage
  - Length of maternal hospital stay

- Fewer NICU admission
- Fewer babies had Apgar scores less than 7[5]
- No evidence of neonatal trauma
- No report on encephalopathy, neurodevelopment at childhood follow-up, breastfeeding at discharge or postnatal depression

Cochrane 2018

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 9, 2018 VOL. 379 NO. 6

Labor Induction versus Expectant Management in Low-Risk Nulliparous Women

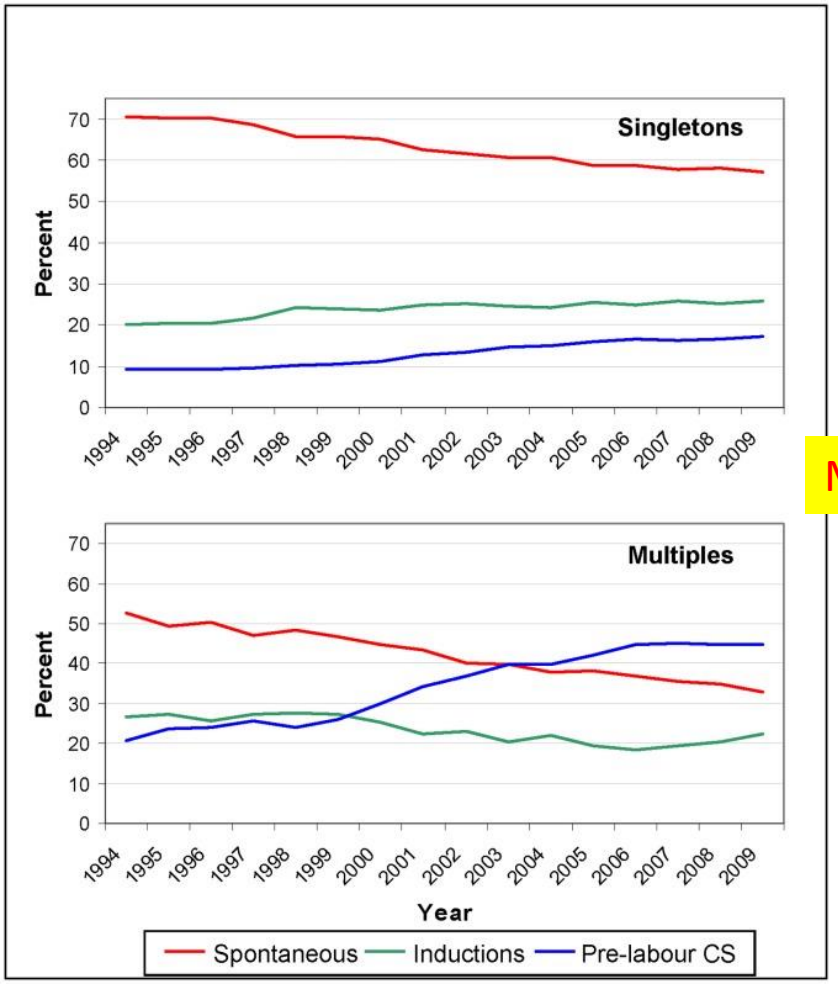
Gestational age 38+0/7 and 38+6/7
Bishop score 24-72 hours after randomization
Expectant management 40+7
IOL at 39.3 vs 40 weeks

A Randomized Research
Large randomized clinical trial – 41 hospitals / 61,006 low risk singleton nulliparas
Elective induction of Labor at 39 weeks or expectant management

39.3 (39+1-39+3) weeks	Delivery	40 (39+3 – 40+7) weeks
9 %	Preeclampsia and Gestational Hypertension	14 %
3 %	Respiratory Support	4 %
4.4 %	Primary Adverse Perinatal Outcome	5.4 %
19 %	Caesarean	22 %

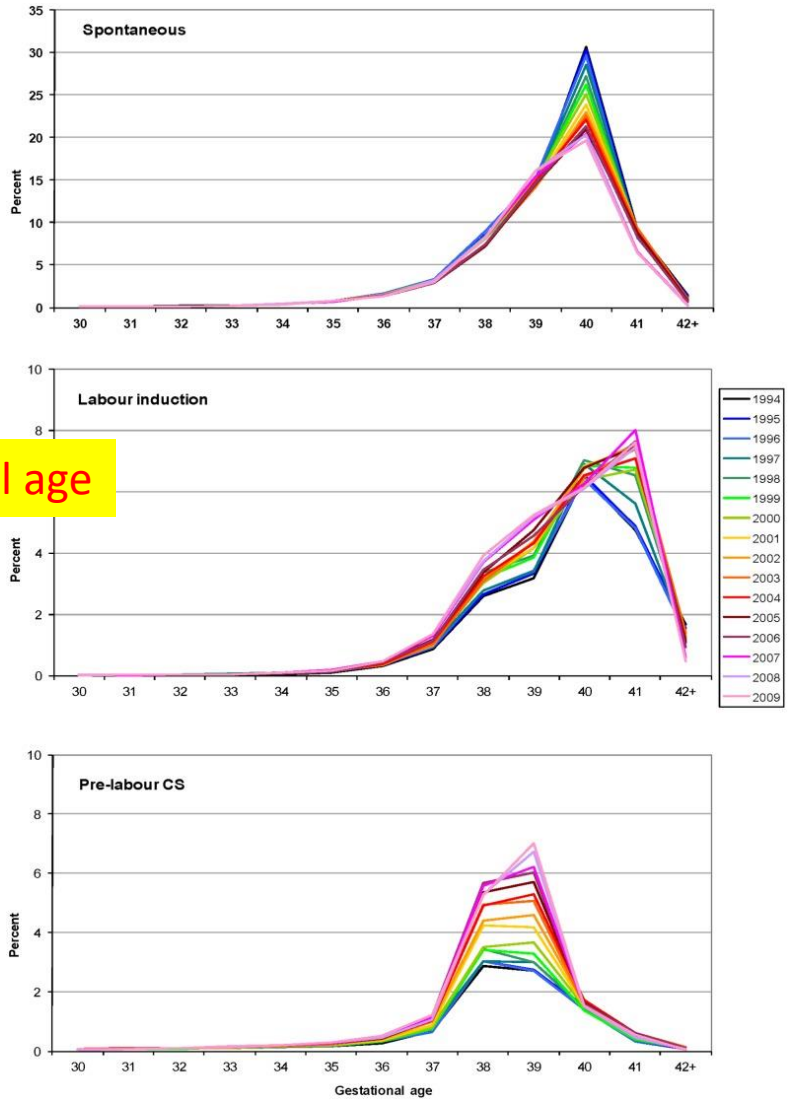
Grobman et al 2018

Trend of Labour



Trend of Gestational Age at Labour

Maternal age



Primipara

Mode of delivery	Gestational age, we 37	38	39	40	41
VE	16	10	6	4	3
Vaginal	7	4	2	2	1.4
Emergency CS	5	3	2	1.3	1.1
Planned CS	3	1.0	0.9	2	0.2

Paediatric:
Individualised risk prediction
Parental counseling,
Planning of optimal timing for discharge
Follow-up visits
Timing of bilirubin determinations, before and after discharge
Other known risk → add important information to overall risk assessment

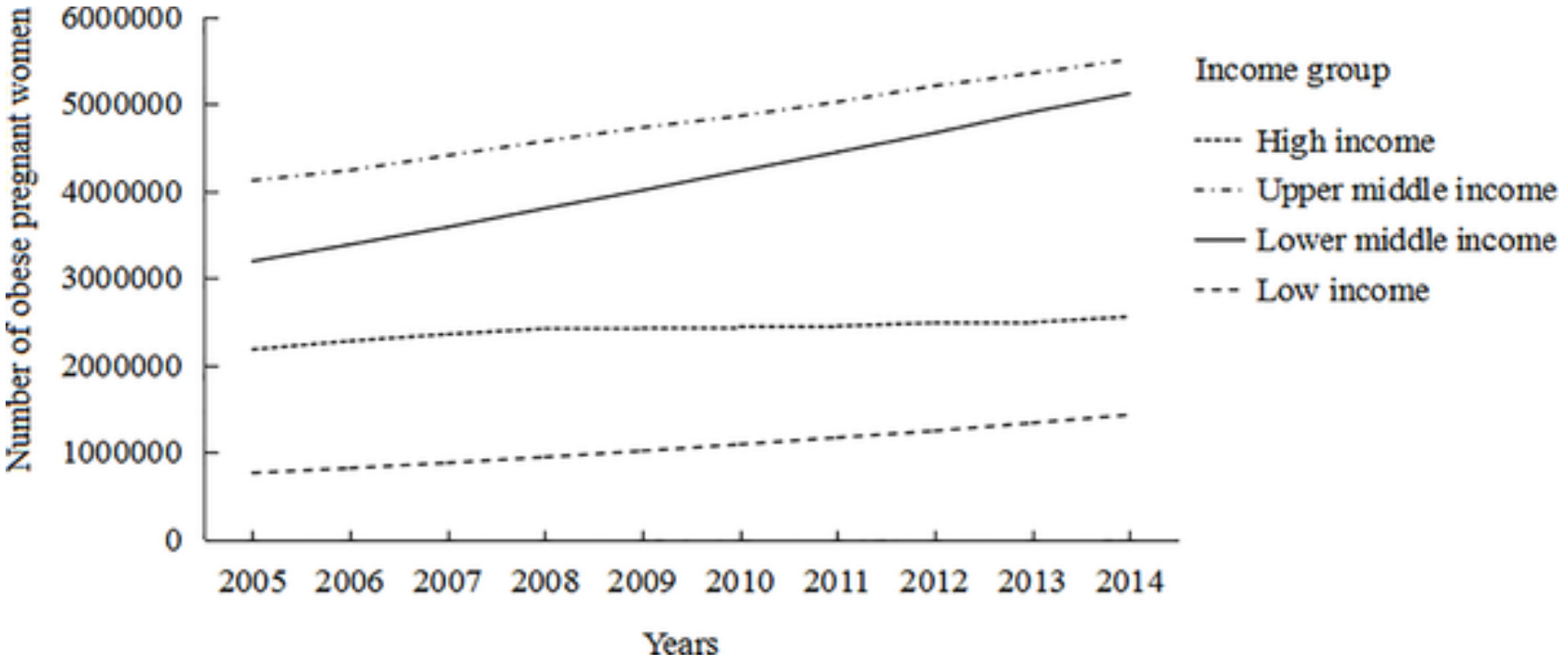
Multi

Mode of delivery	Gestational age, weeks 37	38	39	40	41	>41
VE	13	7	4	3	1.4	1.4
Vaginal	4	2	1.0	0.8	0.7	0.8
Emergency CS	3	2	1.1	1.0	1.1	0.9
Planned CS	2	1.2	0.7	0.6	0.3	0.5

Incidence of neonatal hyperbilirubinemia:
Very high > 10 % (dark red)
High 5 % - 10 % (red)
Moderate > 1 % - < 5 % (yellow)
Low ≤ 1 % (green)

Risk factor sheet targeting prediction of nonhemolytic Hyperbilirubinemia for different combinations of maternal and Obstetric risk factors based on cohort 1 261 948 infants with 23 711 patients

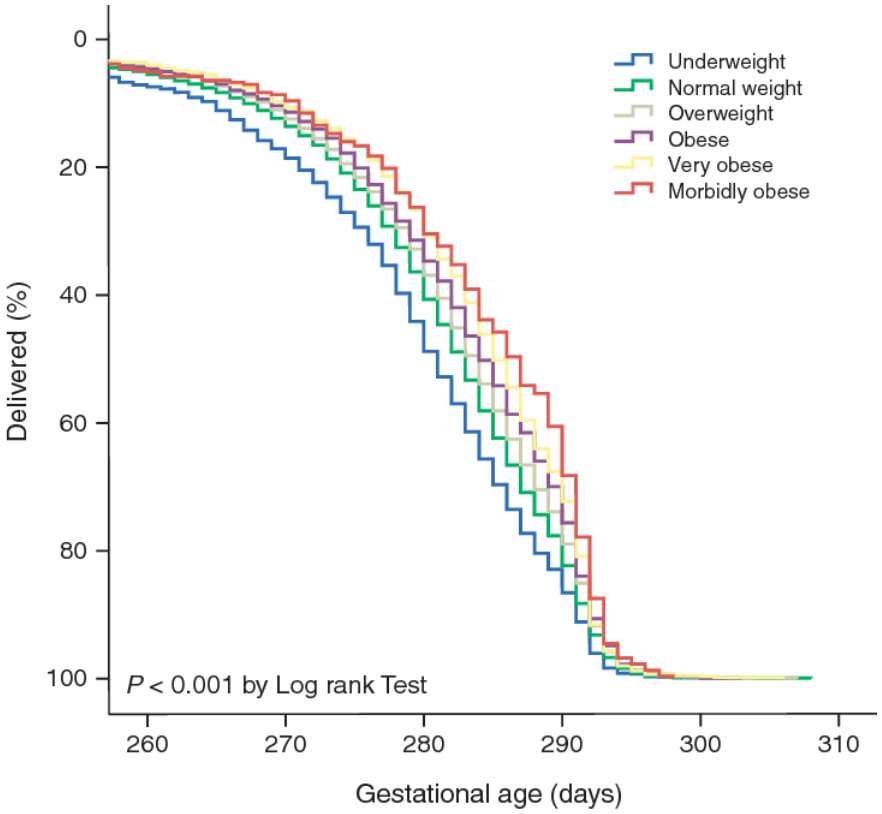
Fig 2. Number of obese pregnant women (BMI≥30) by WHO region from 2005 to 2014.



Chen C, Xu X, Yan Y (2018) Estimated global overweight and obesity burden in pregnant women based on panel data model. PLOS ONE 13(8): e0202183. https://doi.org/10.1371/journal.pone.0202183
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0202183

Overweight/obese mother

Mode of delivery	Gestational age, weeks					
	37	38	39	40	41	>41
VE	19	10	6	4	3	3
Vaginal	8	4	2	1.5	1.2	1.2
Emergency CS	5	3	2	2	1.4	1.3
Planned CS	3	2	0.8	2	1.0	1.2



Obese
Prolonged pregnancy
IOL
Em Caesarean
Fetal Macrosomia

Paediatrics 2015
Arrowsmith BJOG 2011

he BMI categories where the event is delivery

Diabetes in Pregnancy

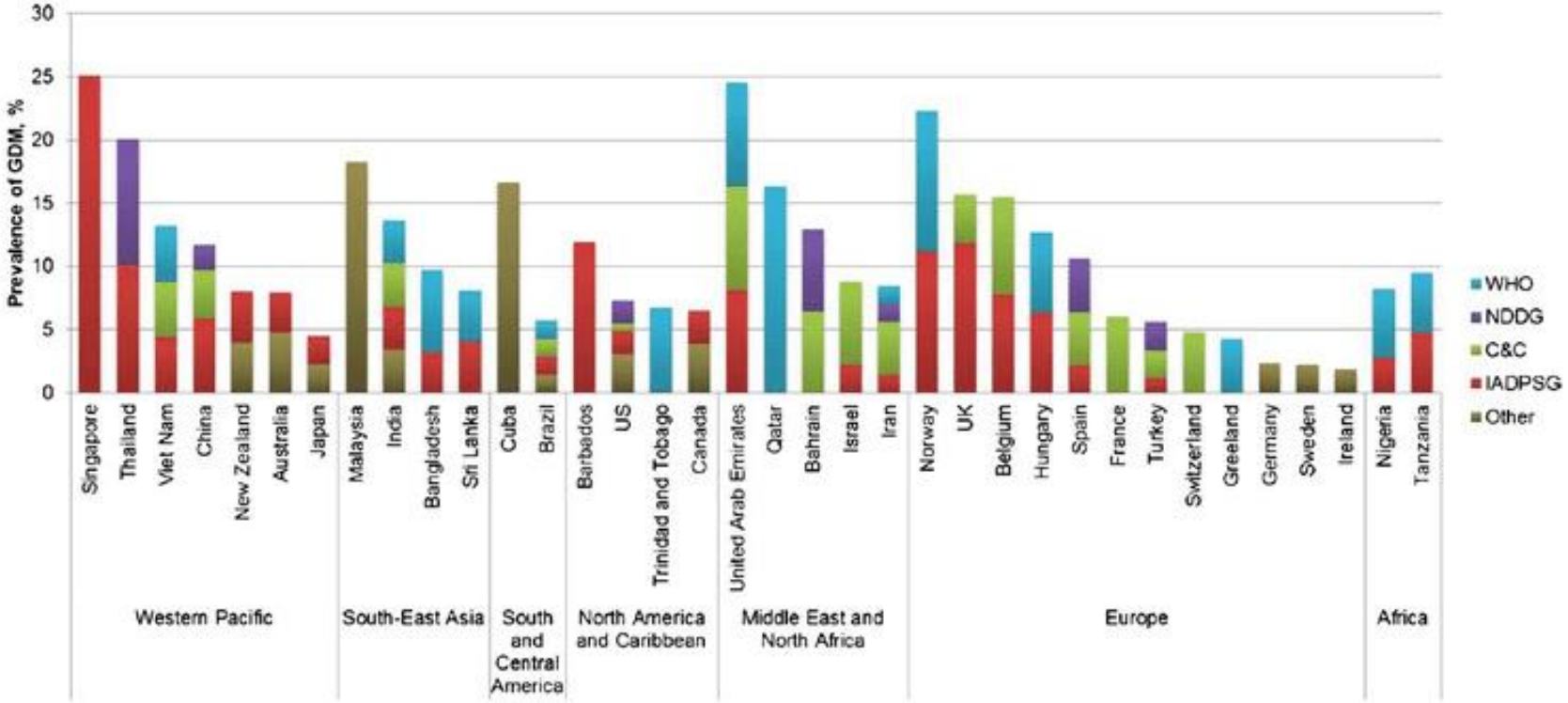
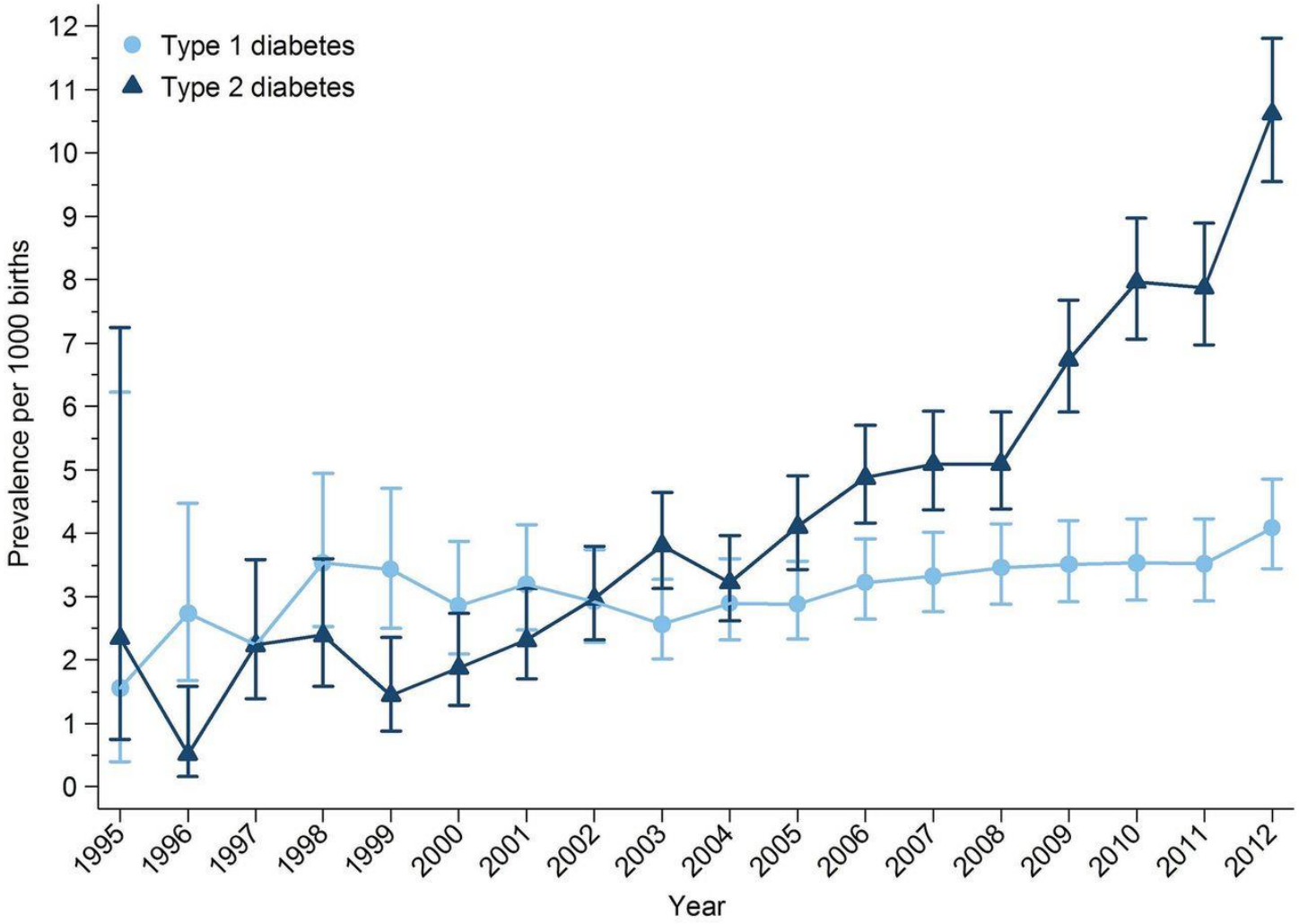


Fig. 2 Country-specific prevalence of GDM according to different diagnostic criteria. *C&C* Carpenter and Coustan criteria, *IADPSG* International Association of Diabetes and Pregnancy Study Groups, *NDDG* National Diabetes Data Group, *WHO* World Health Organization, other included International Classification of Diseases codes and local guidelines or criteria

Prevalence of pregestational diabetes mellitus in pregnancy by year and diabetes type.



Sonia J Coton et al. BMJ Open 2016;6:e009494

BMJ Open

LGA-infants

	Gestational age, weeks					
Mode of delivery	37	38	39	40	41	>41
VE	22	17	8	6	2	2
Vaginal	12	6	3	2	1.2	0.7
Emergency CS	6	4	2	2	1.0	2
Planned CS	5	2	1.2	0.7	0.0	0.0

Incidence of neonatal hyperbilirubinemia:
Very high > 10 % (dark red)
High 5 % - 10 % (red)
Moderate > 1 % - < 5 % (yellow)
Low ≤ 1 % (green)

Risk factor sheet targeting prediction of nonhemolytic Hyperbilirubinemia for different combinations of maternal and Obstetric risk factors based on cohort 1 261 948 infants with 23 711 patients

Diabetes
IOL
Vaginal

39 weeks –3 % Severe NNJ

Asian mother

Mode of delivery	Gestational age, weeks					
	37	38	39	40	41	>41
VE	22	14	8	7	8	7
Vaginal	8	5	4	3	3	2
Emergency CS	6	3	4	3	2	1.2
Planned CS	3	1.0	0.6	1.0	2	3

Incidence of neonatal hyperbilirubinemia:
Very high > 10 % (dark red)
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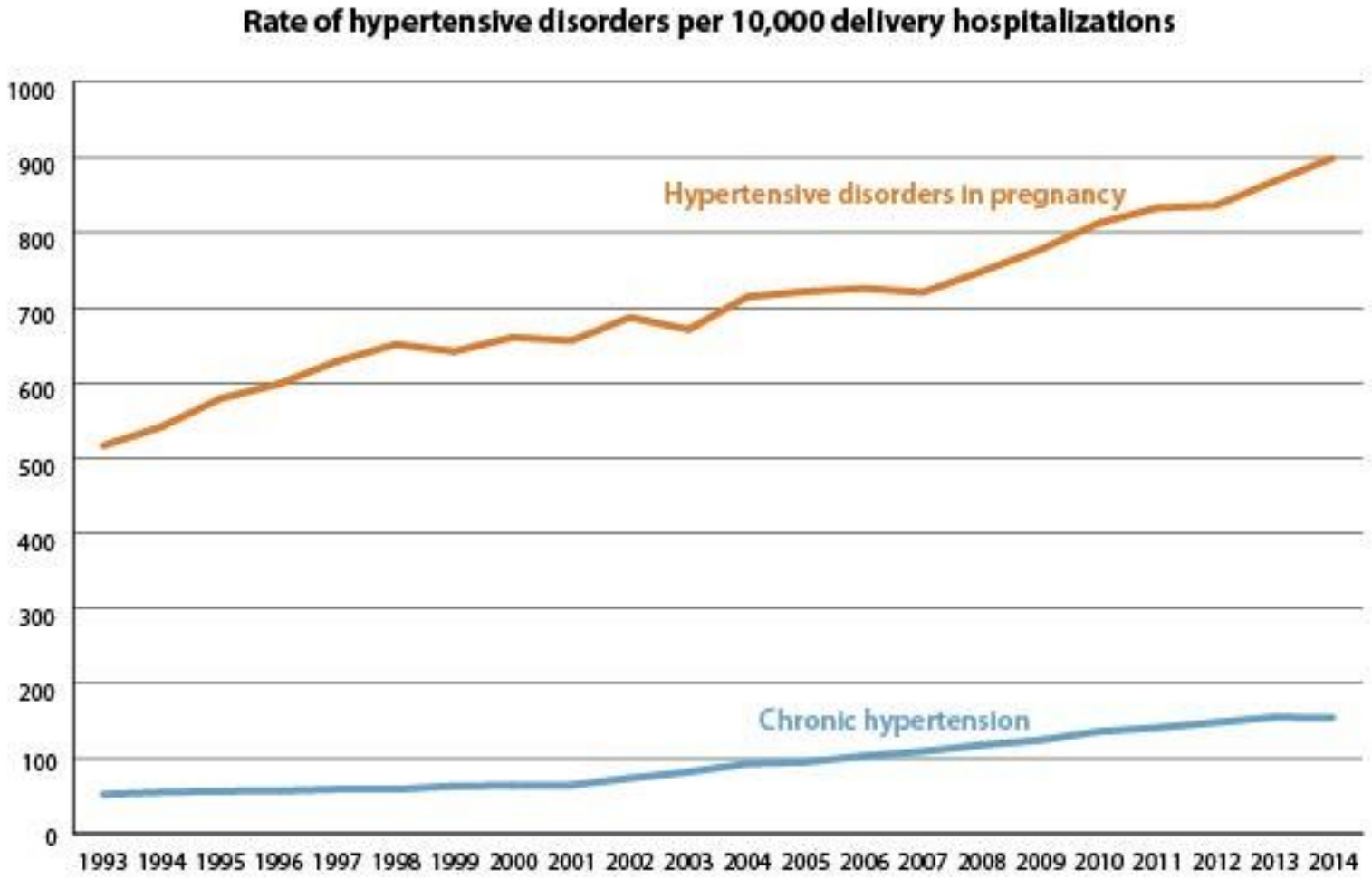
Low ≤ 1 % (green)

Risk factor sheet targeting prediction of nonhemolytic Hyperbilirubinemia for different combinations of maternal and Obstetric risk factors based on cohort 1 261 948 infants with 23 711 patients

Planned Caesarean?
39 weeks

Paediatric:
Individualised risk prediction
Parental counseling,
Planning of optimal timing for discharge
Follow-up visits
Timing of bilirubin determinations, before and after discharge
Other known risk → add important inormation to overall risk assessment



CDC and Prevention

SGA-infants

Mode of delivery	Gestational age, weeks					
	37	38	39	40	41	>41
VE	16	12	7	5	5	5
Vaginal	8	5	3	2	2	2
Emergency CS	7	6	4	4	2	2
Planned CS	5	3	4	6	1.0	4

Risk factor sheet targeting prediction of nonhemolytic Hyperbilirubinemia for different combinations of maternal and Obstetric risk factors based on cohort 1 261 948 infants with 23 711 patients

Incidence of neonatal hyperbilirubinemia:
Very high > 10 % (dark red)
High 5 % - 10 % (red)
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Genetic – SLCO1B1 ?

SLCO1B1

Predispose subjects to neonatal hyperbilirubinemia by limiting hepatic bilirubin uptake.

The impact of SLCO1B1 genetic polymorphisms on neonatal hyperbilirubinemia: a systematic review with meta-analysis

CONCLUSION: This study demonstrated that the 388 G>A mutation of the SLCO1B1 gene is a risk factor for developing neonatal hyperbilirubinemia in Chinese neonates, but not in white, Thai, Brazilian, or Malaysian populations; the SLCO1B1 521 T>C mutation provides protection for neonatal hyperbilirubinemia in Chinese neonates, but not in white, Thai, Brazilian, or Malaysian populations..

Malaysian J Pathol 2009; 31(2) : 99 – 104

ORIGINAL ARTICLE

Variants of organic anion transporter polypeptide 2 gene are not risk factors associated with severe neonatal hyperbilirubinemia

Fei-Liang WONG *BSc (Hons)*, *Nem-Yun BOO *MBBS, FRCP*, AINOON Othman *MBBS*, *Dr Med Sc*, and *May-Kay WANG *MBBS, MMed*

Liu, J. Pediatr. 2013

Summary

- **The trend of obstetric practice has influence in development of SNNJ.**
- **History**
  - **Obstetrics risk (Ethnicity + Gp O + Rhesus negative + Diabetes + Siblings SNNJ + antibody + BMI + Parity + Mode of delivery)**
  - **Neonatal risk (GA + BW + G6PD + Lactation failure + cephalhaematoma + jaundice within 24 hrs)**
- **Timed TSB – best available method**
- **Genetic – not for Malaysian Chinese**
- **History + Timed TSB + Genetic → ? Detection rate**

Thank You