

10th World Congress of Perinatal Medicine in Developing Countries
14:00, June 4th, 2022
Intercontinental Hotel, Punta Cana, Dominican Republic

14.00- 15.30	PERINATAL CARE FAOPS SESSION	
	Efforts to improve infants health care in Japan Satoshi Kusuda	
	First trimester tragedy Laila Arjumand	
	Journey of tocolysis Milind Shah	
	Cost effective interventions to improve newborn outcomes Ranjan Pejaver	
	Discussant: Satoshi Kusuda	
Punta Cana	COFFEE BREAK	

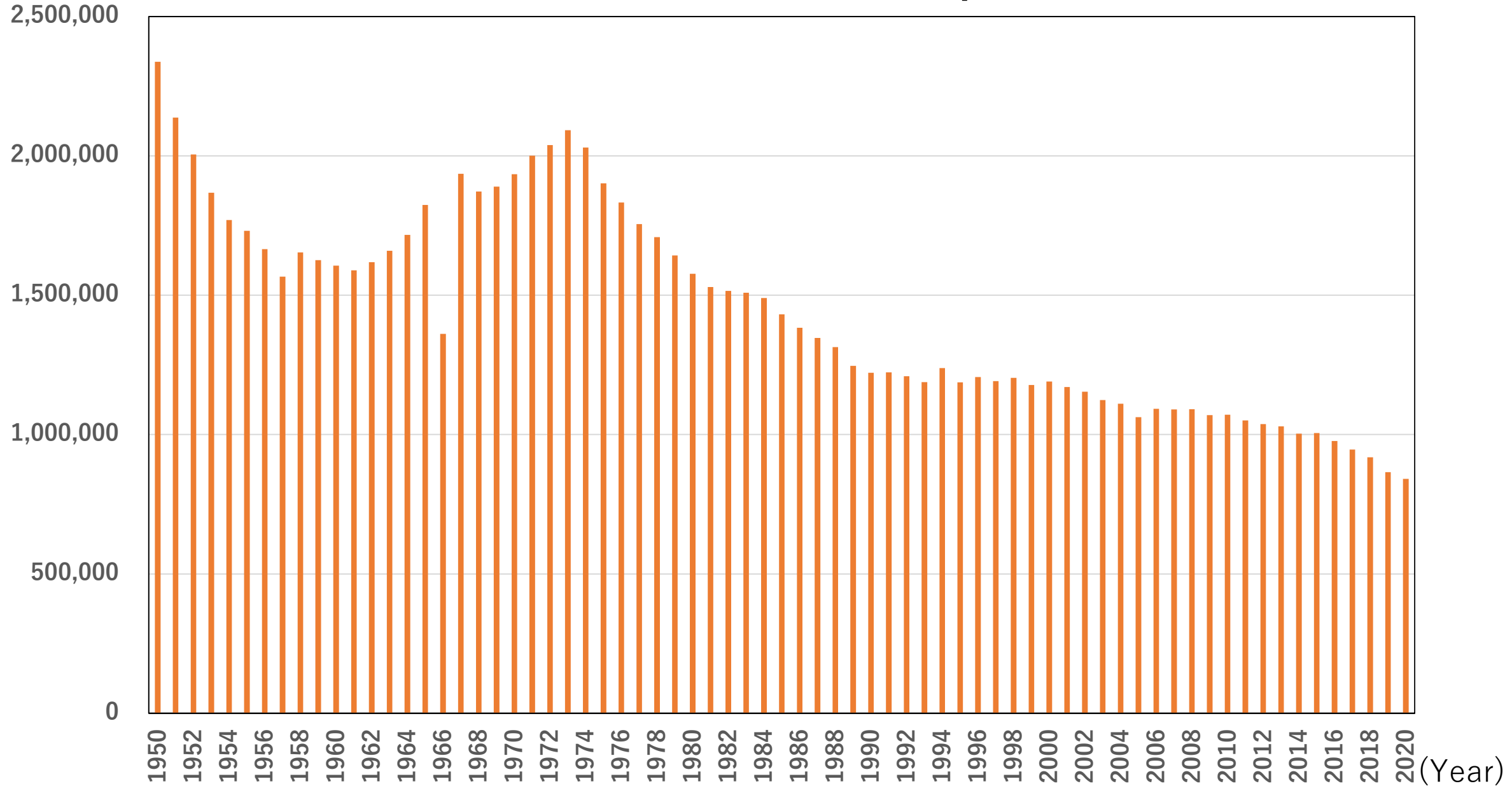
Efforts to improve infant health care in Japan

Satoshi Kusuda
Kyorin University
Tokyo, Japan

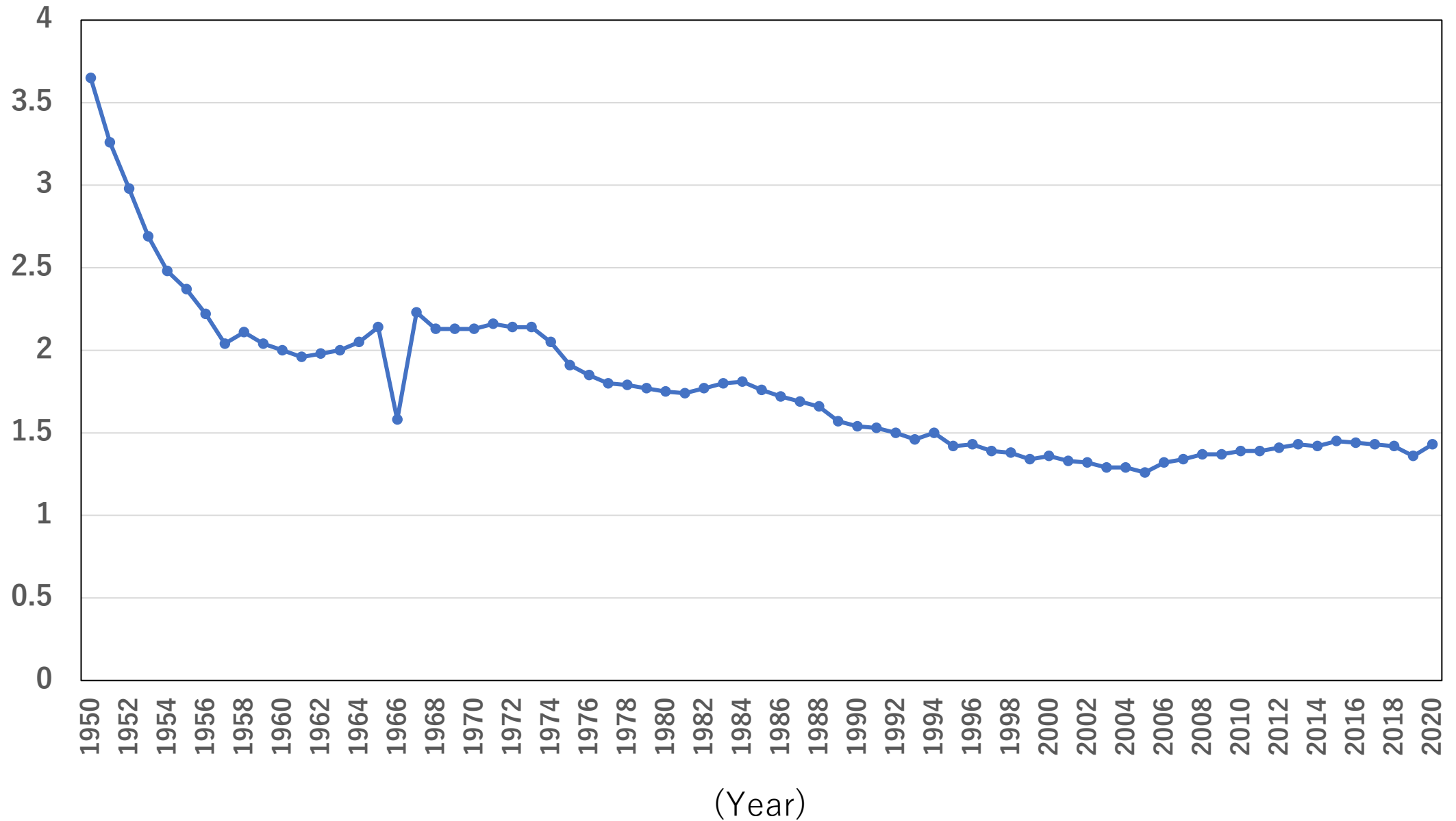
Overview

- Health levels among infants in Japan
- History of infant health care

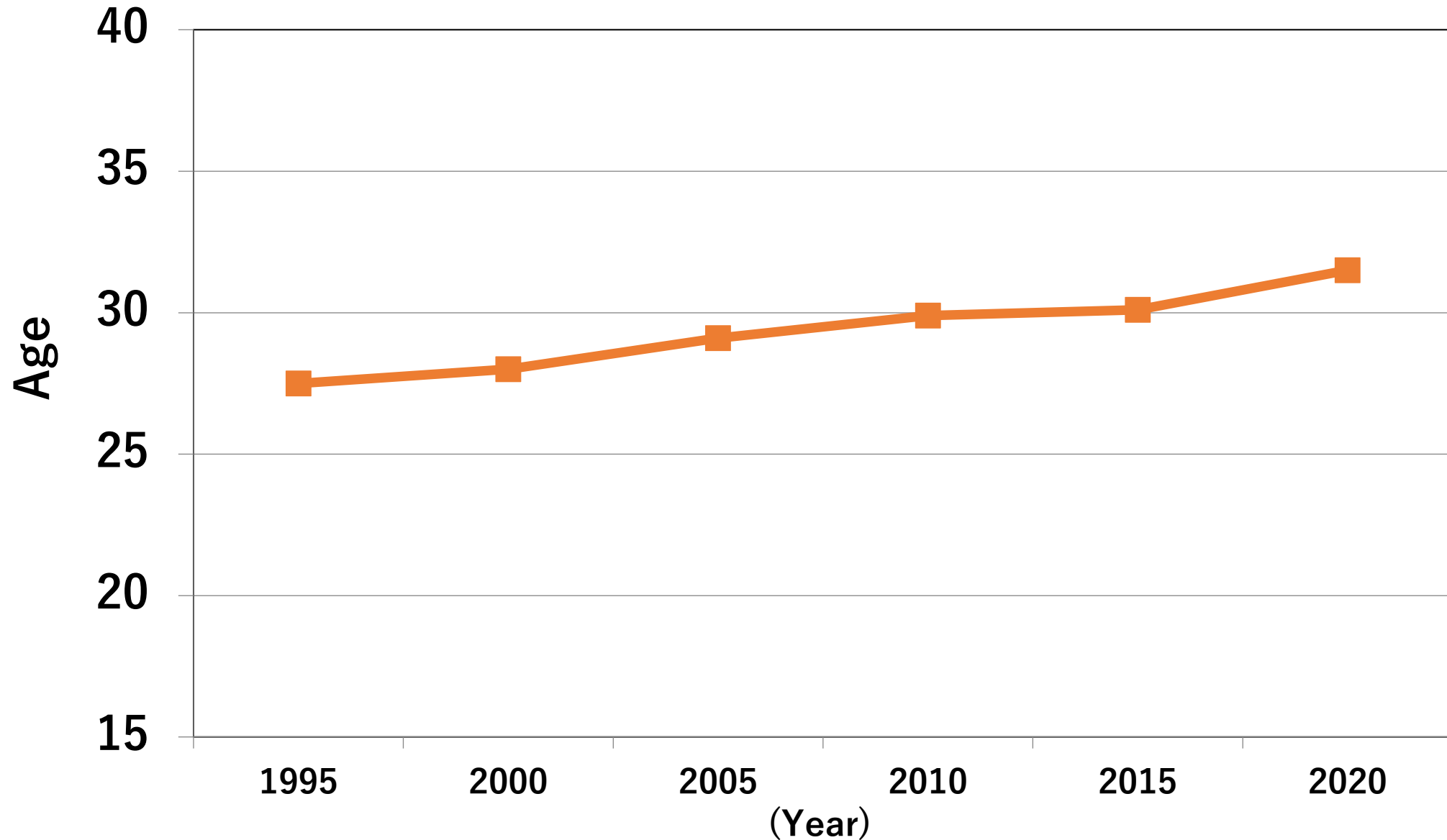
Number of live birth in Japan



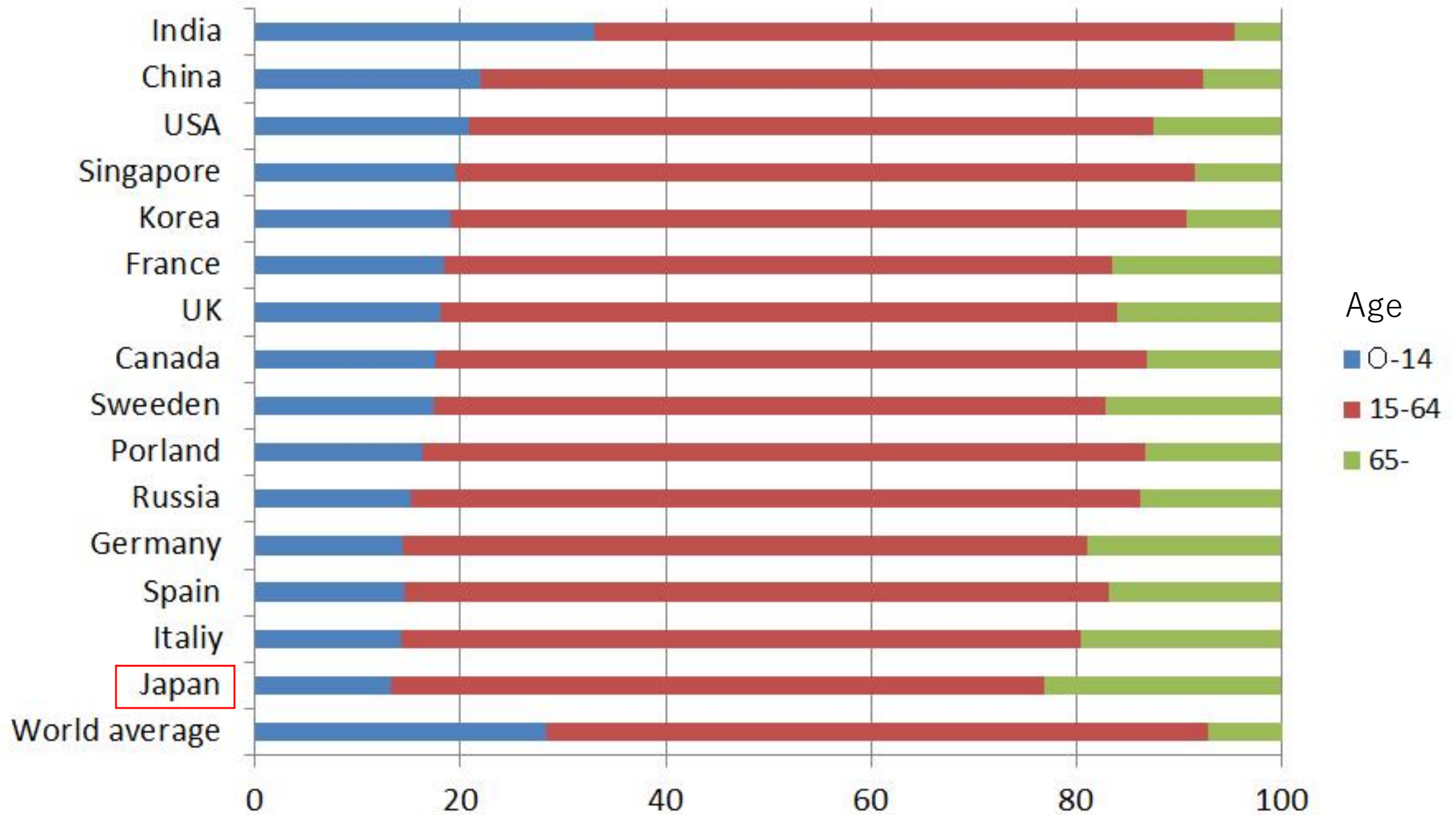
Trends in total fertility rate



Maternal mean age bearing first child

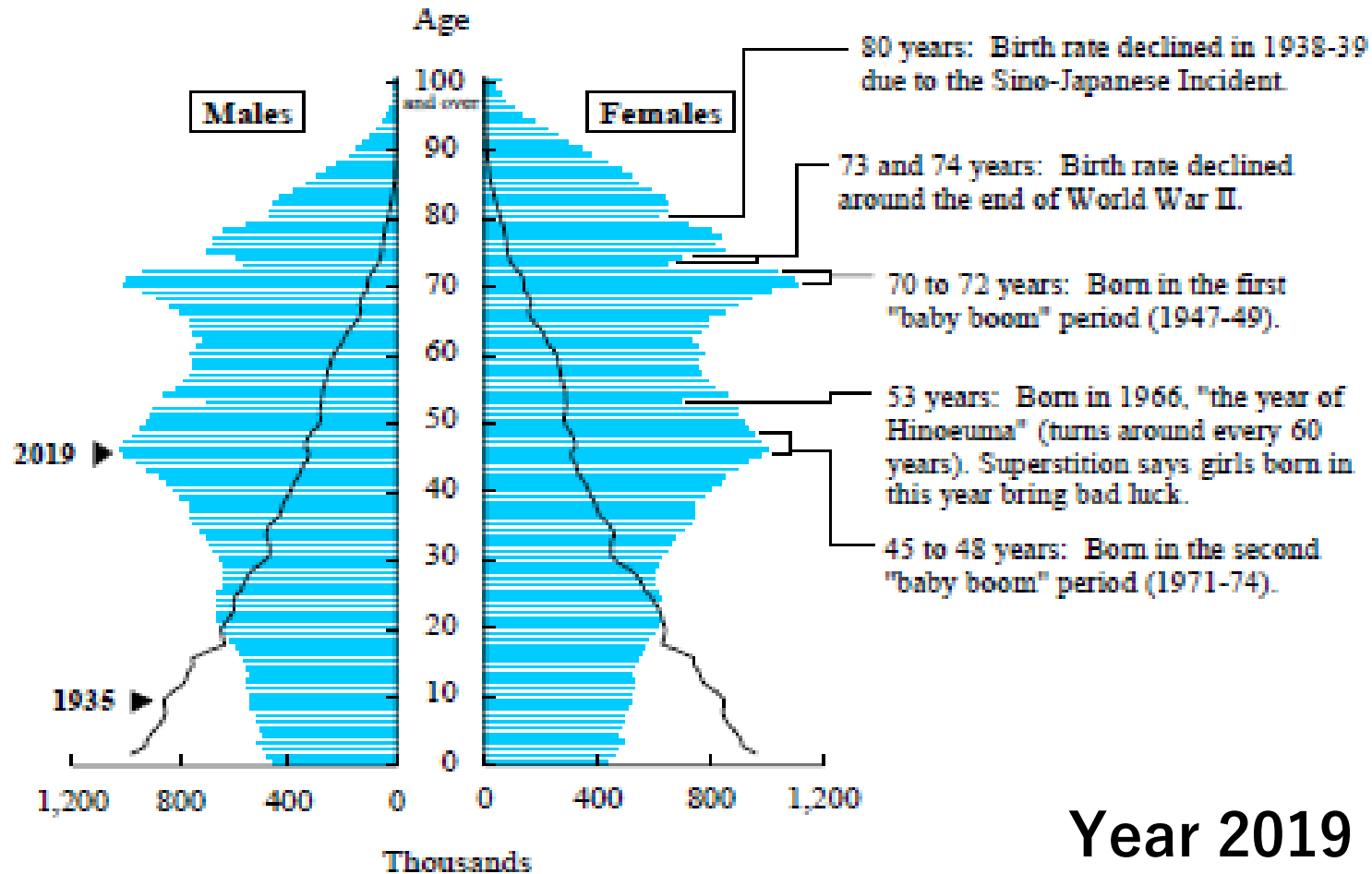


Population by age in different countries



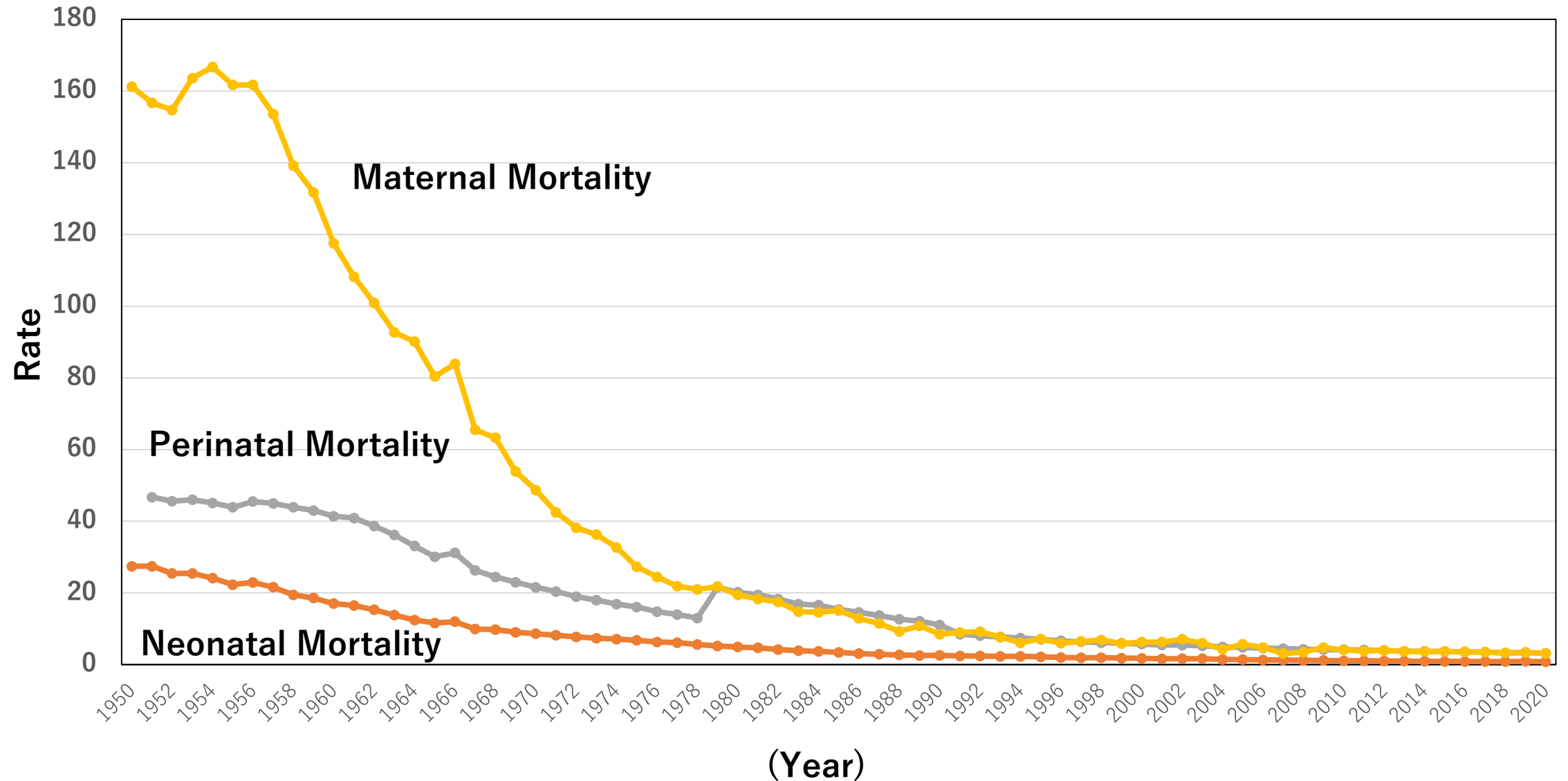
Population pyramid

Figure 2.1
Population Pyramid

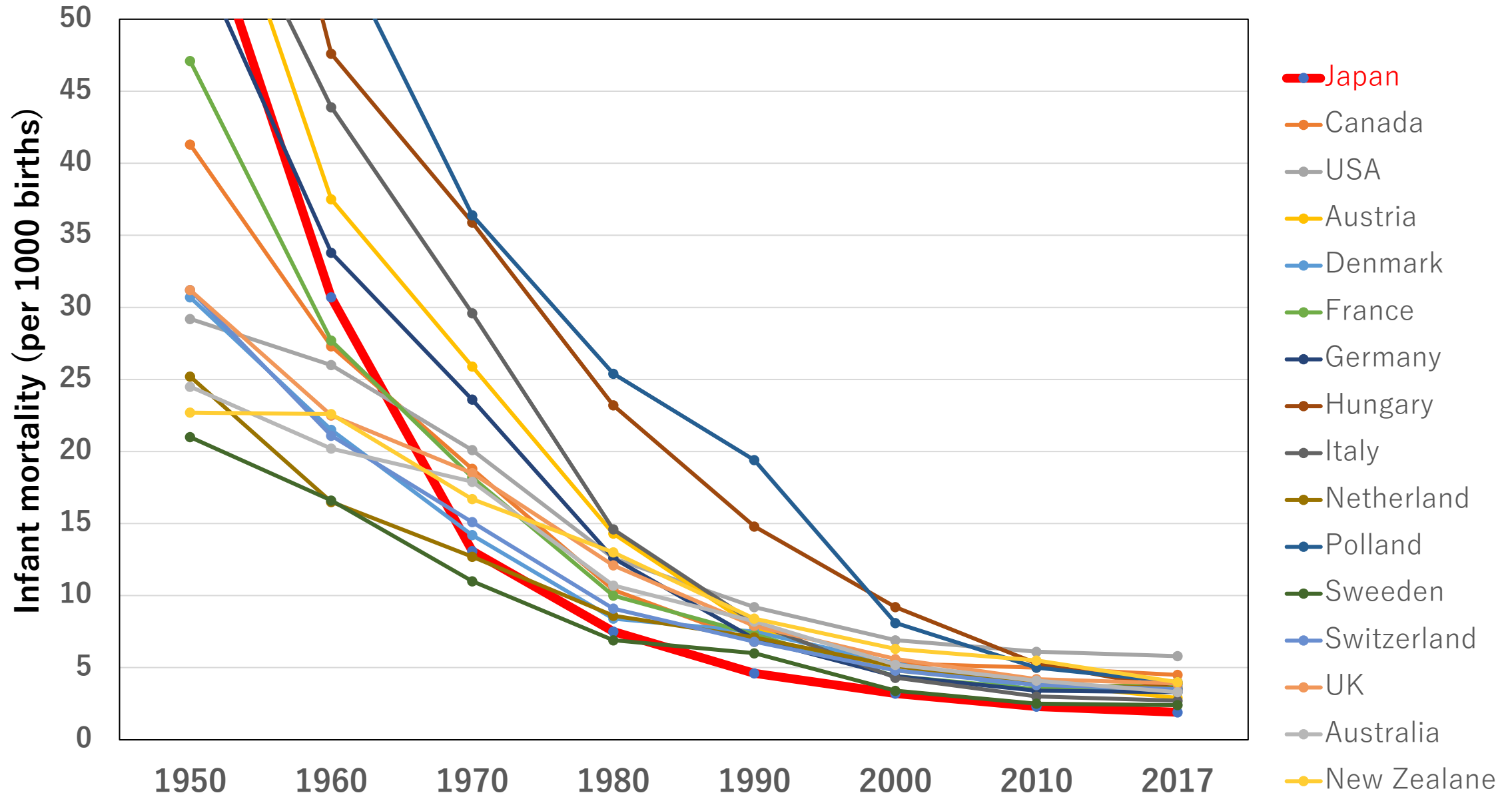


Source: Statistics Bureau, MIC.

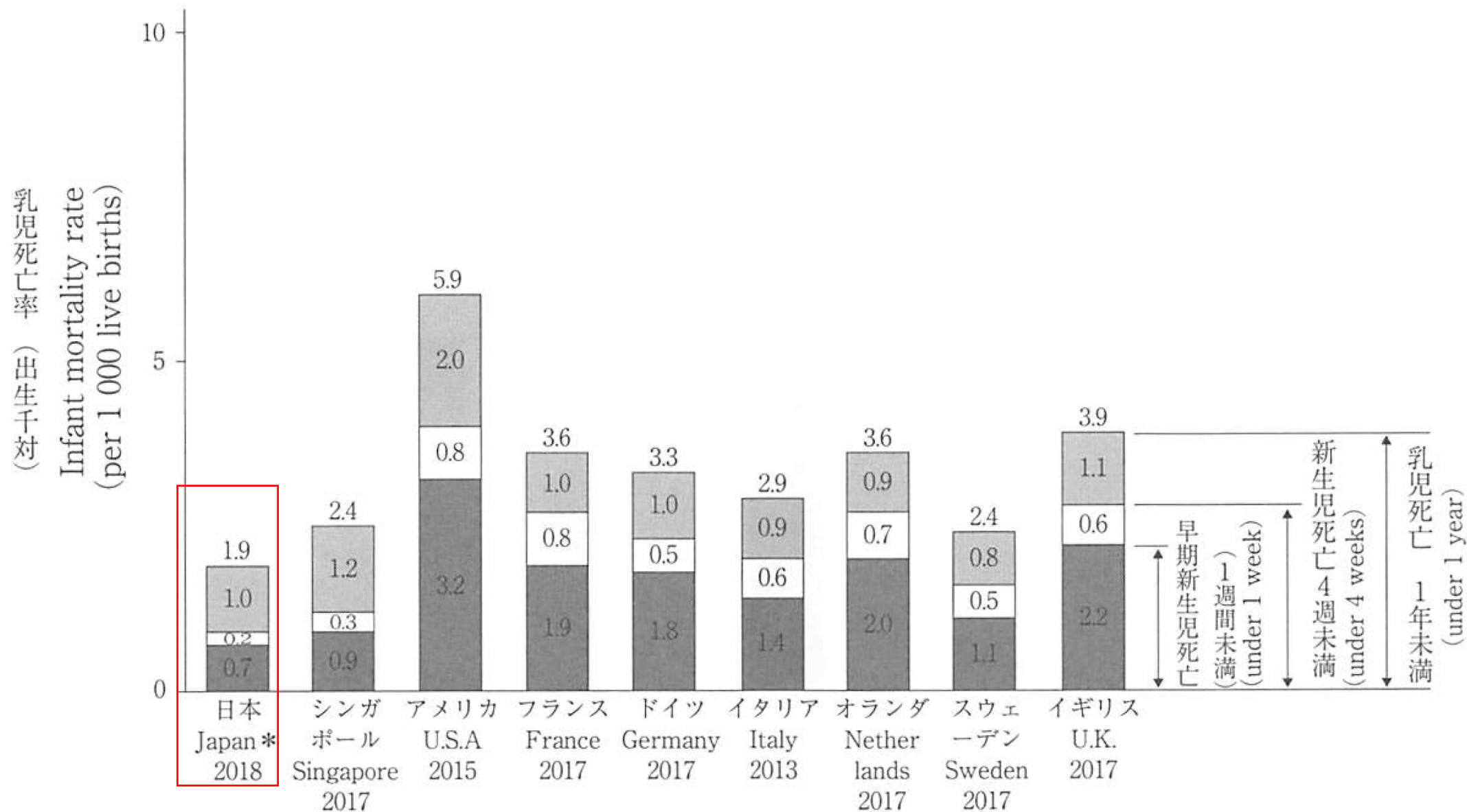
Trends in maternal, perinatal, and neonatal mortality rates



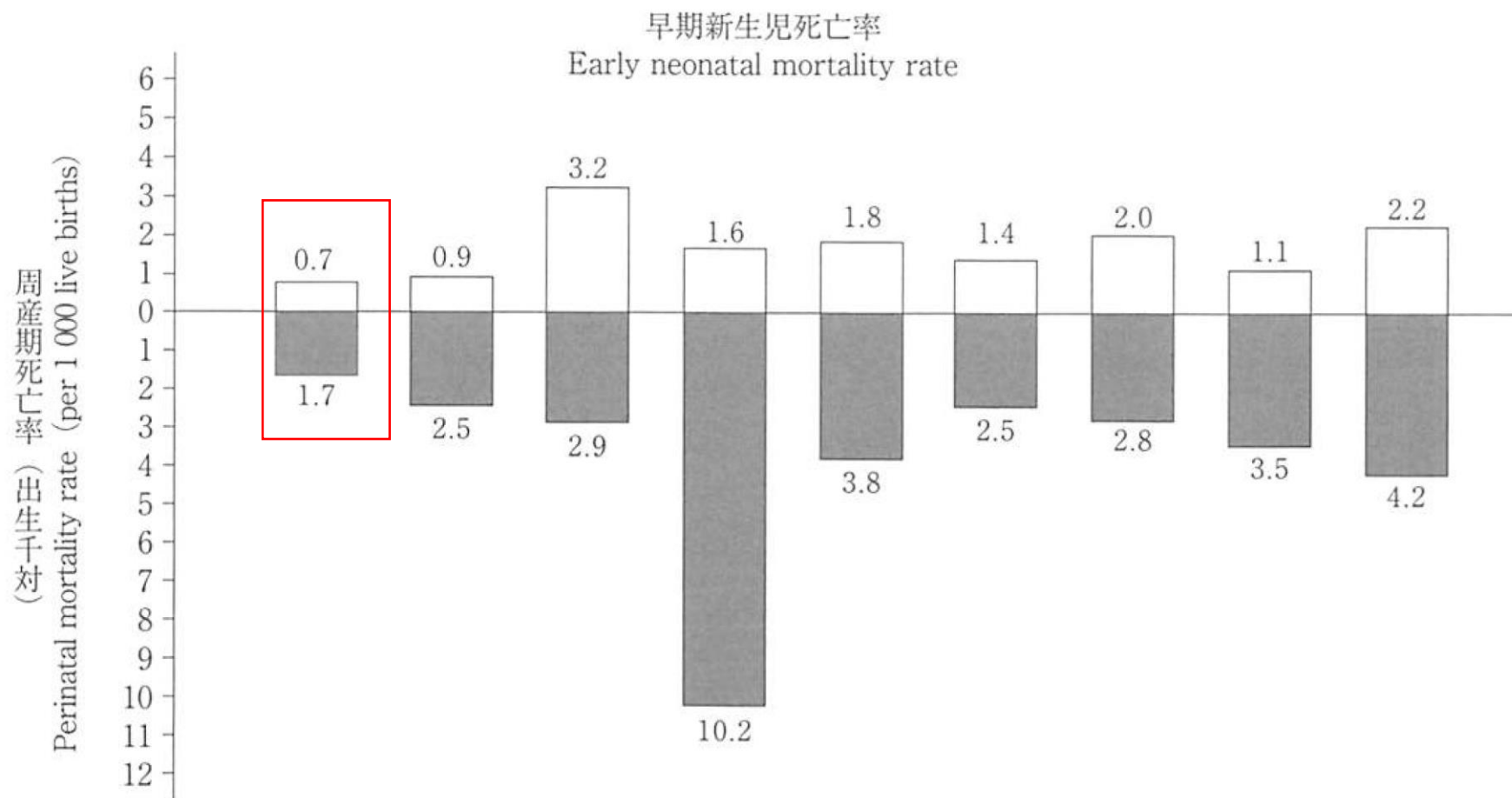
International comparison of infant mortality



Comparison of infant mortality rate in selected countries



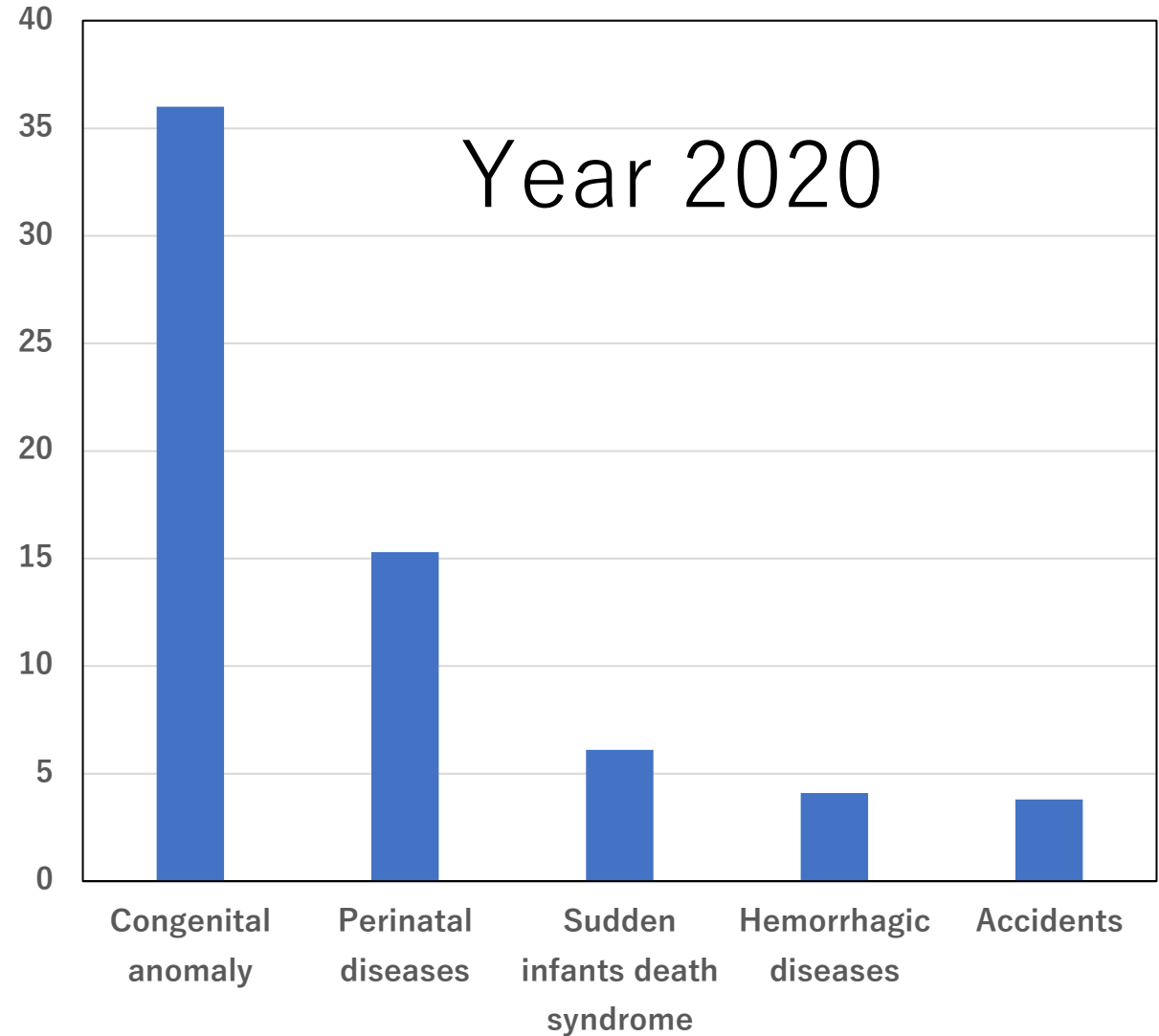
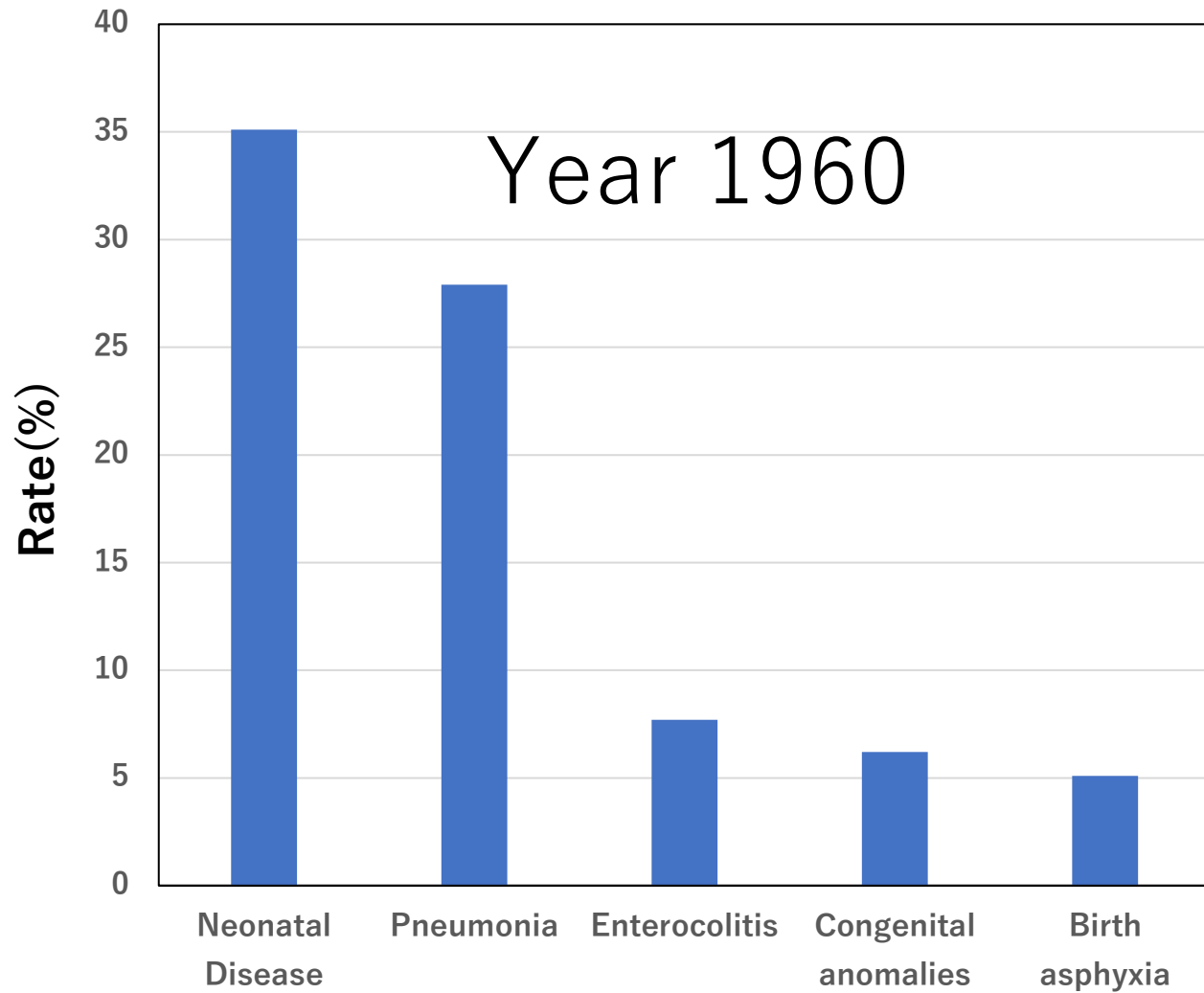
Comparison of perinatal mortality rate in selected countries



妊娠28週以後の死産比
Foetal death ratio at 28 weeks and over of gestation

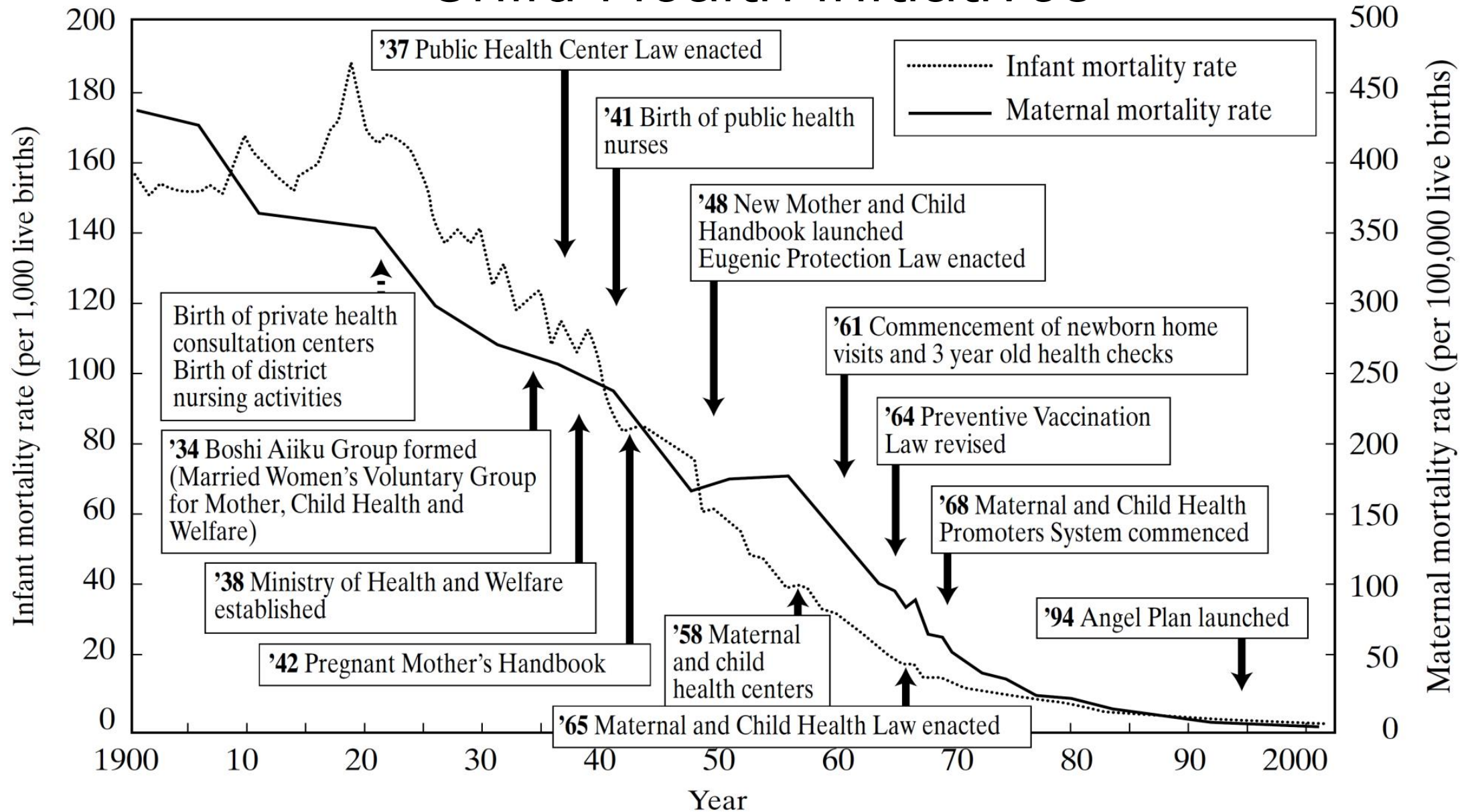
日本	シンガポール	アメリカ	フランス	ドイツ	イタリア	オランダ	スウェーデン	イギリス
Japan*	Singapore	U.S.A.	France	Germany	Italy	Netherlands	Sweden	U.K.
2018	2017	2015	2010	2017	2013	2017	2017	2017

Comparison of causes of infant death between 1960 and 2020

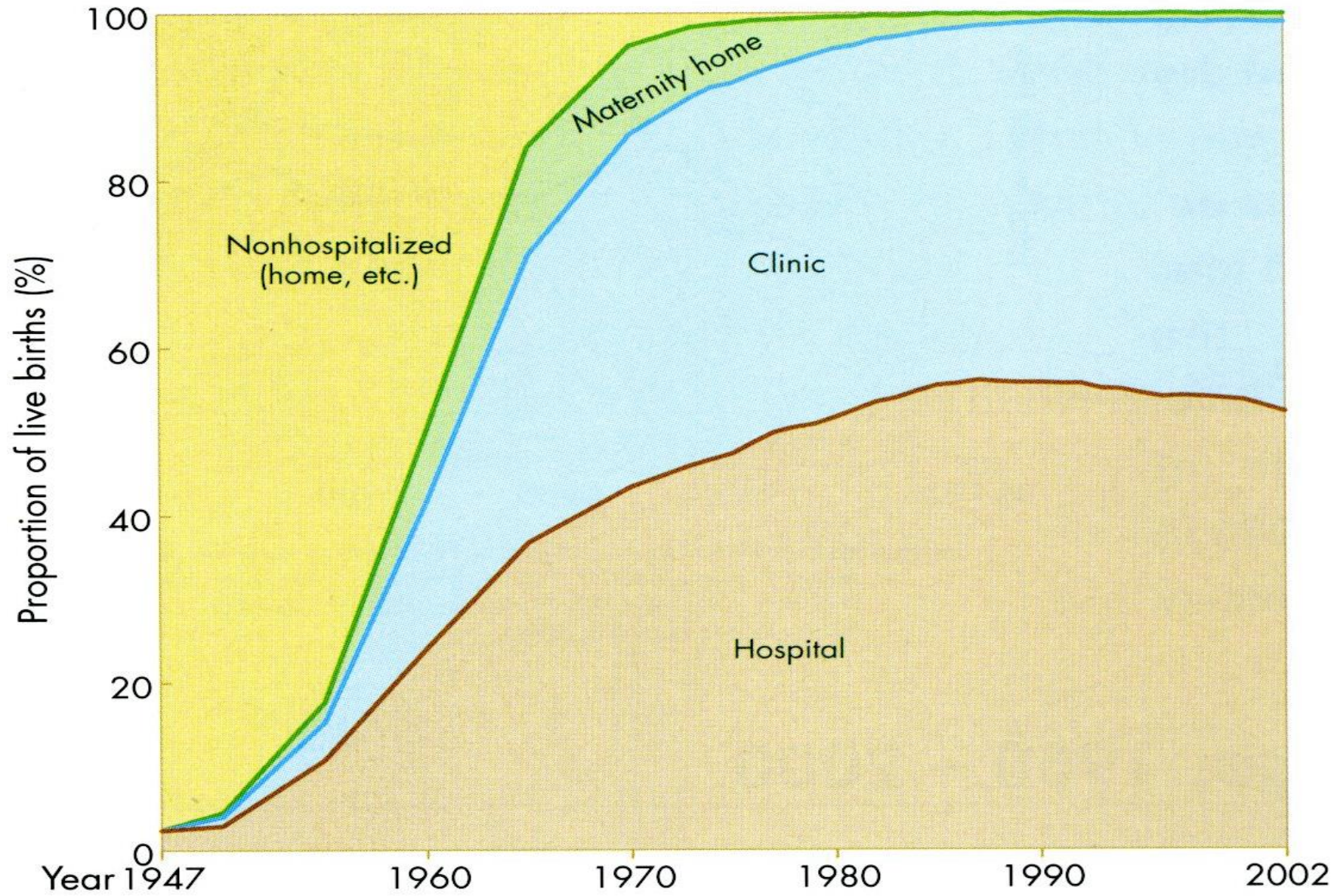


History of infant health care

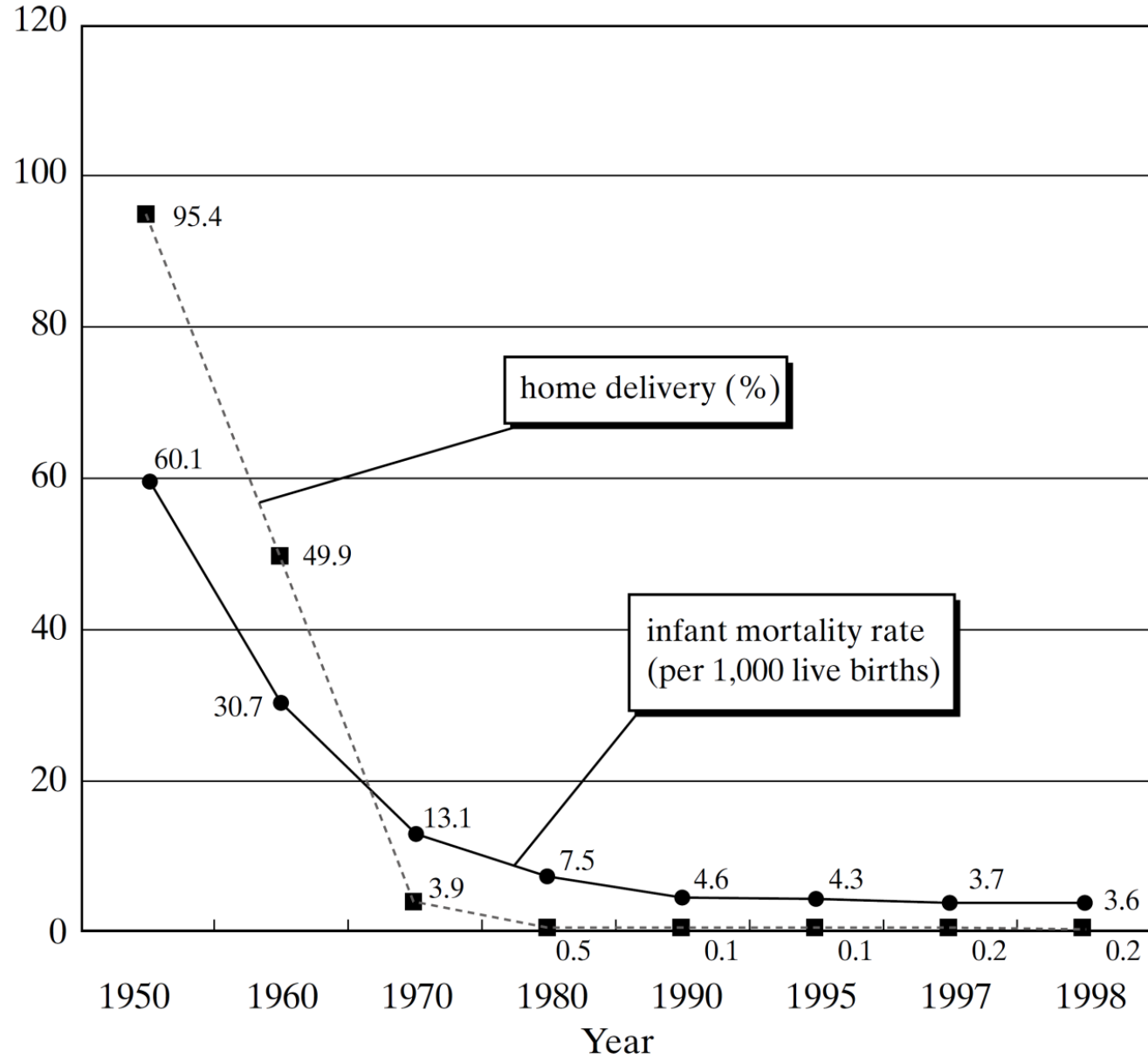
Infant mortality, maternal mortality and Maternal and Child Health initiatives



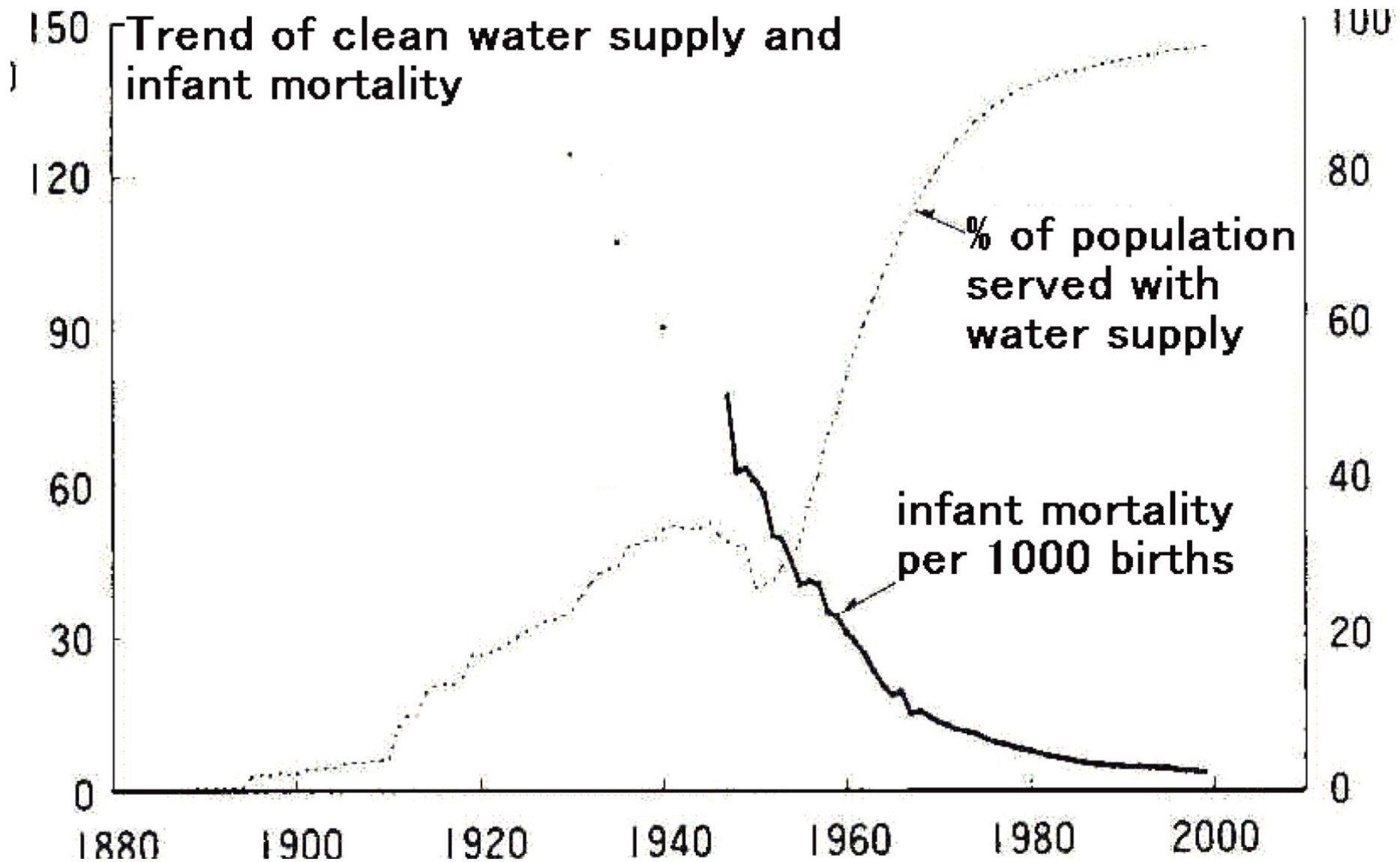
Change of birthplace



Changes in home delivery and infant mortality



Clean water supply and infant mortality



Maternal and Child Health Handbook (Boshi Techo)

- Launched in 1941
- The pregnancy/after-delivery health guidance program
- Outreaching health advice for pregnant and post-delivery mothers
- Outreaching health guidance for newborns
- Infants' medical examinations
- Child rearing classes
- Child rearing consultation
- Vaccination guidance

Maternal and Child Health Handbook English version

英語版

**Maternal and Child
Health Handbook**
母子健康手帳



Issued on Year Month Day
 年 月 日交付

Name of Parent(s)/Guardian(s)
保護者の氏名：
:

Name of Child Order of Birth
子の氏名 (第 子)

No. _____

Services for mothers received with the Maternal and Child Health Handbook

- Stated in 1942
- Currently, health check-ups are offered for pregnant mothers at public expense for 14 times during their pregnancy, at appointed healthcare facilities.

Services for infants received with the Maternal and Child Health Handbook

- Started in 1948
- Infants' medical examinations are held at public expense at appointed medical institutions, for three times in total, at 2 weeks, 4 months, and 10 months of age.
- Free vaccinations

Before birth

Diagnosis of pregnancy by physician



Submission of notification of pregnancy

(Submitted to municipality where the expectant mother resides.)



Issuance of Maternal and Child Health Handbook

(Issued to expectant mother by municipality in which she resides.)



Antenatal checkup

* In most municipalities, the cost of this examination is covered by public funds (2 times). Often a coupon is given that entitles the expectant mother to receive an antenatal checkup. It is given together with Maternal and Child Health Handbook when a notification of pregnancy has been submitted.

Special education for expectant mothers and their spouses

Prenatal visit



Childbirth

After birth

Childbirth

Submission of register of childbirth to the registrar of the municipality

Issuance of childbirth notification to the municipal health center

Examination for congenital metabolic disorder

* There are local governments that provide hearing examinations for newborn infants.

If necessary, medical aid program for premature babies

Home-visit guidance for newborns

Infant checkup

If necessary, very detailed checkup

Vaccination

(See schedule for vaccinations.)

Health checkup of young child

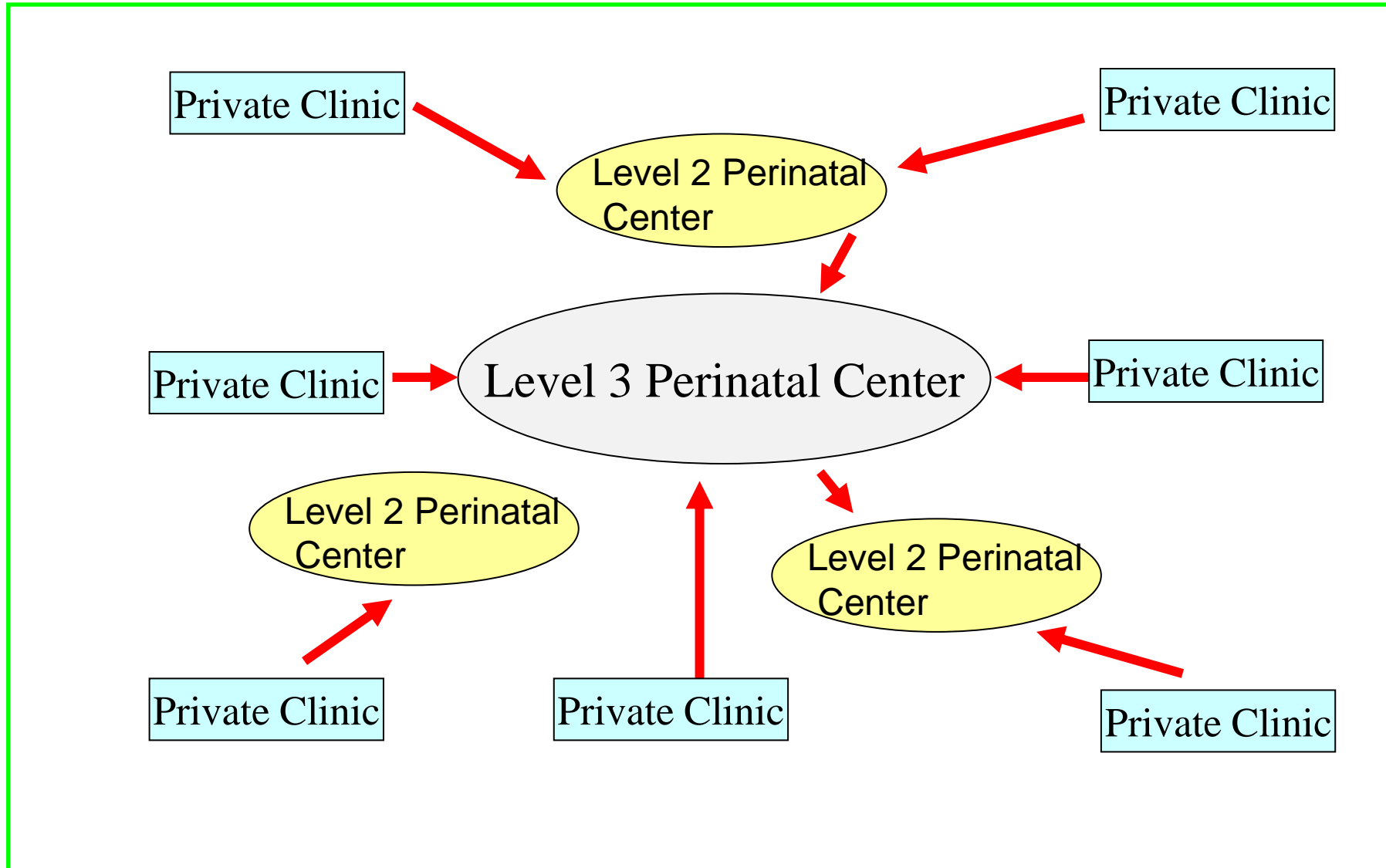
If necessary, very detailed checkup

Universal health insurance system

- Since 1961 Japan has provided universal health coverage, which allows virtually all access to preventive, curative and rehabilitative services at an affordable cost.
- For infants, all medical cost is covered by the health insurance system and government subsidy.

Perinatal Network System (started in 1994)

Population: 1 million, Birth: 10 thousands, LBW: 1,000



Summary

- Health care level for infants in Japan is well organized
- In order to achieve it, the role of health care system and government supports are essential
- Maternal and Child Health Handbook played crucial roles
- High risk perinatal care also progressed with the establishment of the nationwide perinatal network system

FIRST TRIMESTER COMPLICATIONS AND MANAGEMENT



PROF LAILA.A. BANU

PAST PRESIDENT- **OGSB**

PRESIDENT-BPS(**BANGLADESH PERINATAL SOCIETY**)

DEPUTY SECRETARY GENERAL (WESTERN REGION)-**FAOPS**



-
- First trimester is the most critical time in pregnancy.

Introduction

- Pregnancy complications
 - More during first trimester (upto 12 weeks gestation)
 - 20-40% of women
- Most commonly
 - Bleeding per vaginum
 - Pain abdomen
- Accurate diagnosis is needed
 - Reassurance to patient if pregnancy is well
 - Appropriate intervention if not
 - Worse prognosis if heavy bleeding or extends into second trimester

Complications of Early Pregnancy

- **Bleeding in first trimester:**

Possible explanations:

- Intrauterine Pregnancy 50%
- Missed abortion 25-30%
- Blighted ovum 20-25%
- Incomplete abortion
- Inevitable abortion
- Complete spontaneous abortion
- Ectopic Pregnancy
- Hydatidiform Mole

Table 3. Differential Diagnosis Of Early Pregnancy Complications

Pregnancy-Related Conditions

Ectopic pregnancy
Spontaneous abortion
Molar pregnancy
Ruptured corpus luteum cyst
Hyperemesis gravidarum
Implantation bleeding

Non-Pregnancy-Related Conditions

Pelvic or urinary infections
Urinary calculus
Appendicitis
Gall bladder disease
Pancreatitis
Hepatitis
Ruptured ovarian cyst
Hemorrhagic ovarian cyst
Ovarian torsion
Trauma to cervix

A. Maternal

I. First-trimester bleeding

Incidence:

29 -36.2%

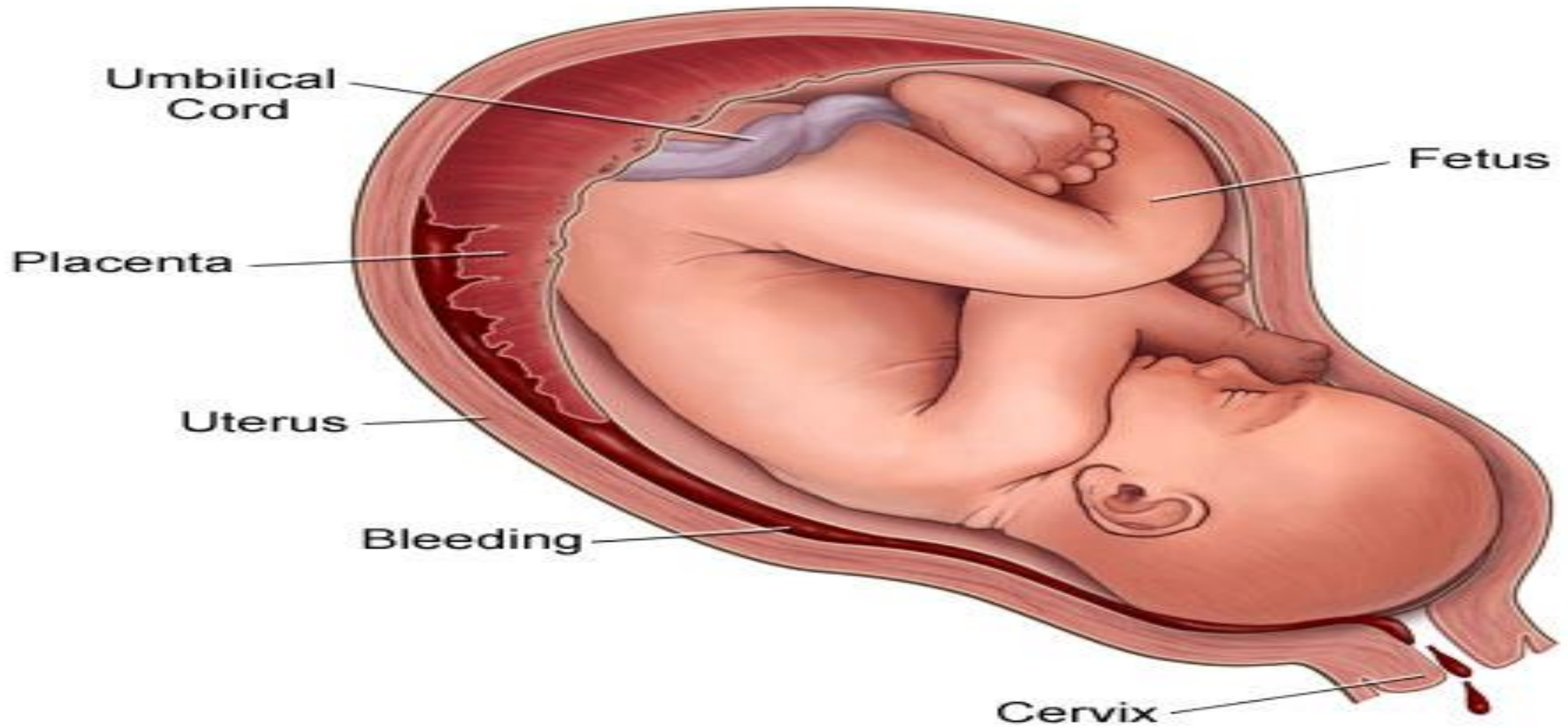
Cause:

A correlation was found with the number of embryos transferred.

Consequence:

1. Increased 2nd trimester & 3rd trimester bleeding
2. PROM
3. Preterm contractions & PTL
4. NICU admissions

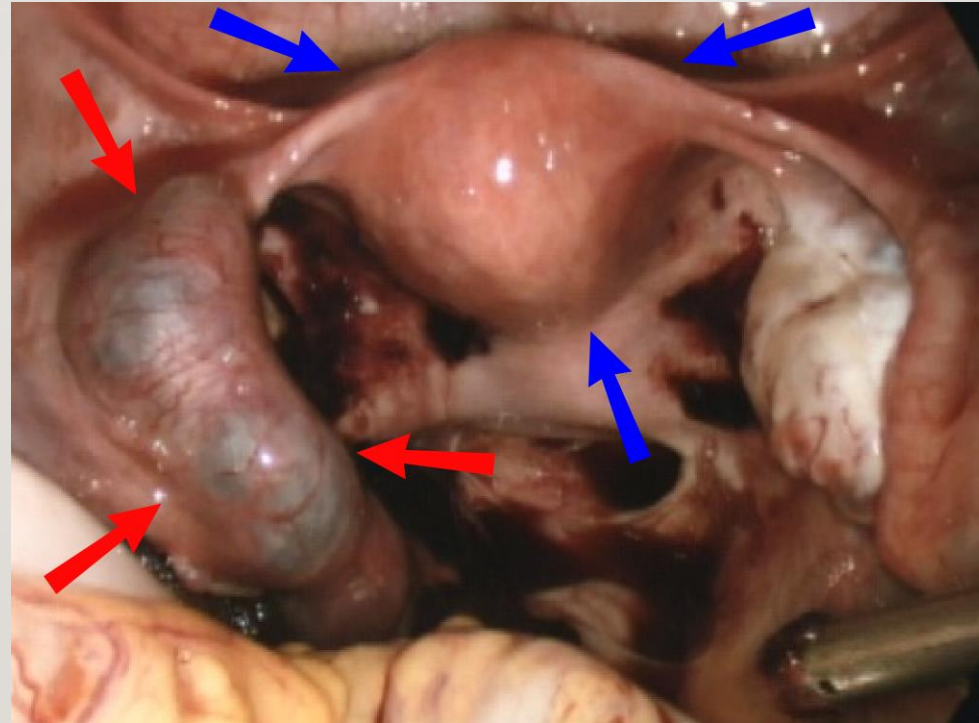
Visible Bleeding



Differential Diagnosis: First Trimester Vaginal Bleeding

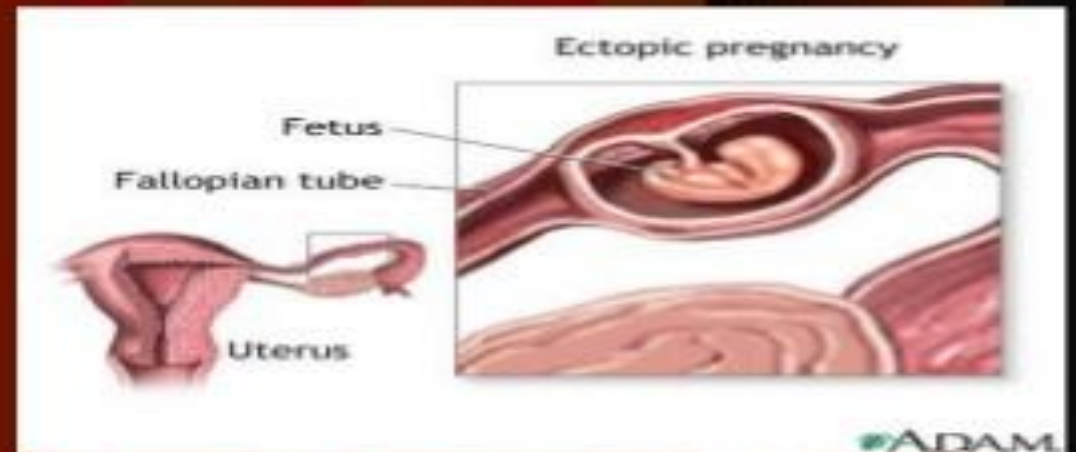
- **Ectopic pregnancy**
- Spontaneous miscarriage
- Idiopathic bleeding in a viable pregnancy
- Molar pregnancy
- Subchorionic hemorrhage
- Infection of the vagina or cervix
- Cervical abnormalities
 - Malignancy, polyps, trauma
- Vaginal trauma

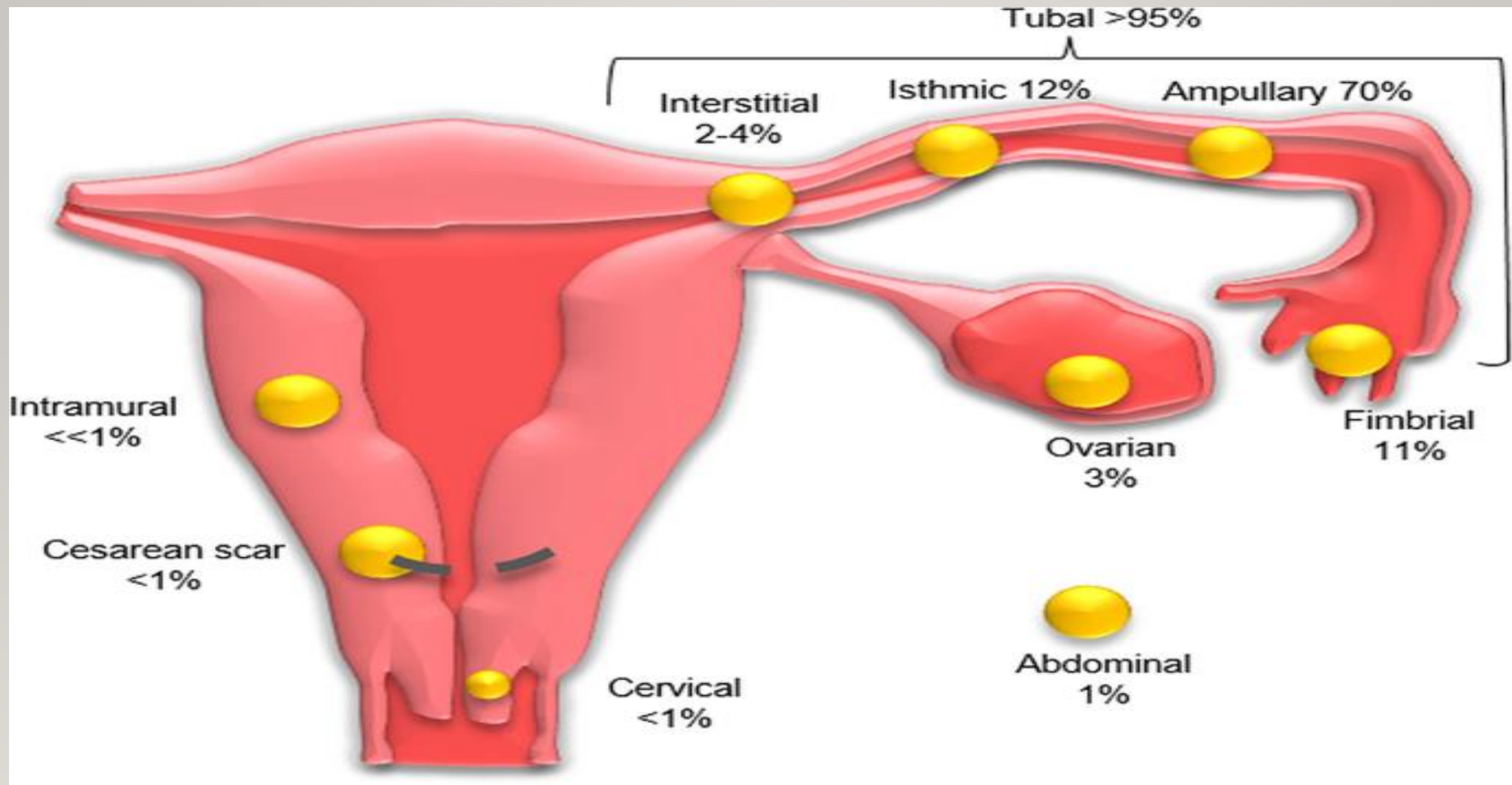
ECTOPIC PREGNANCY

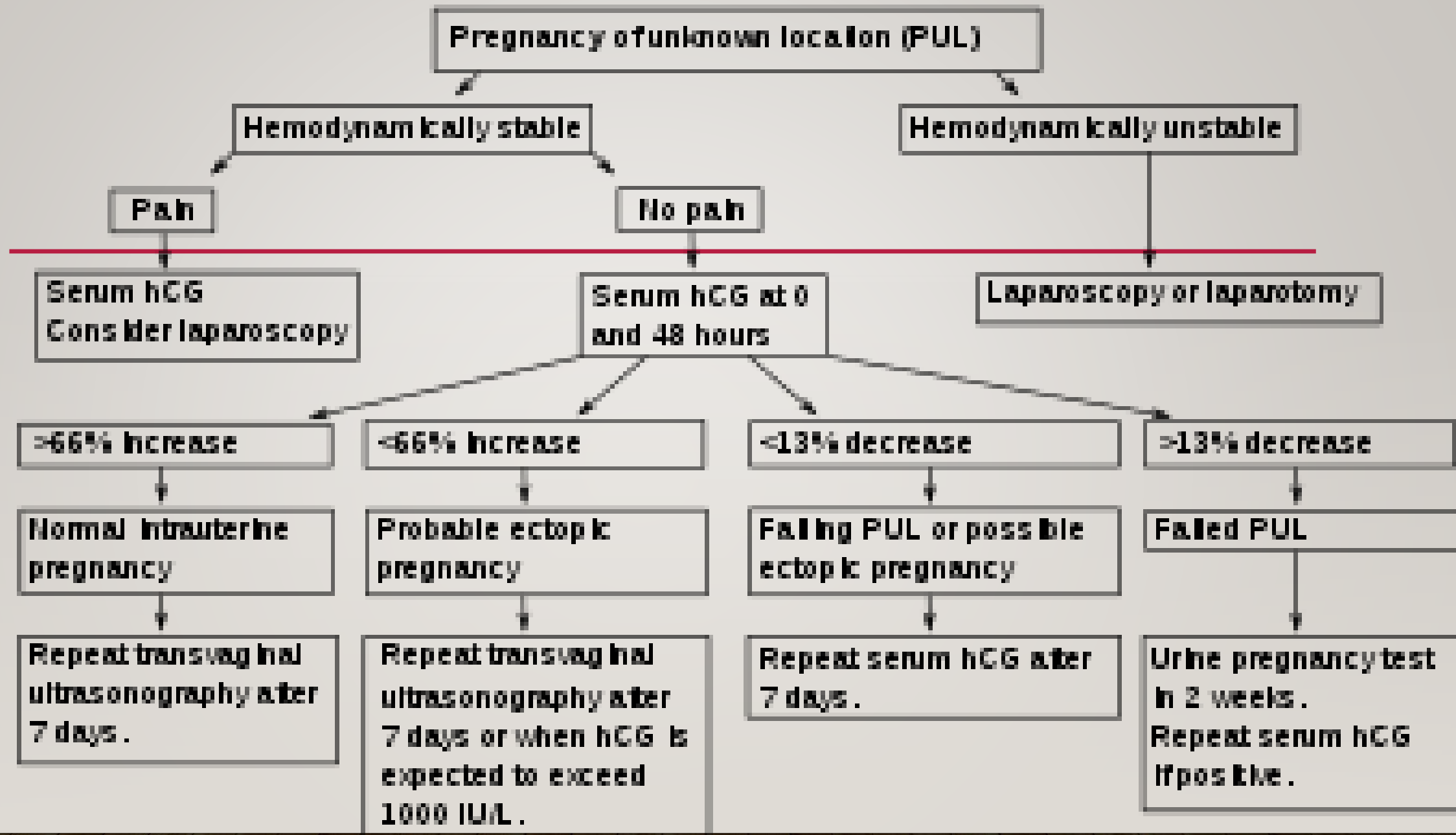


Definition

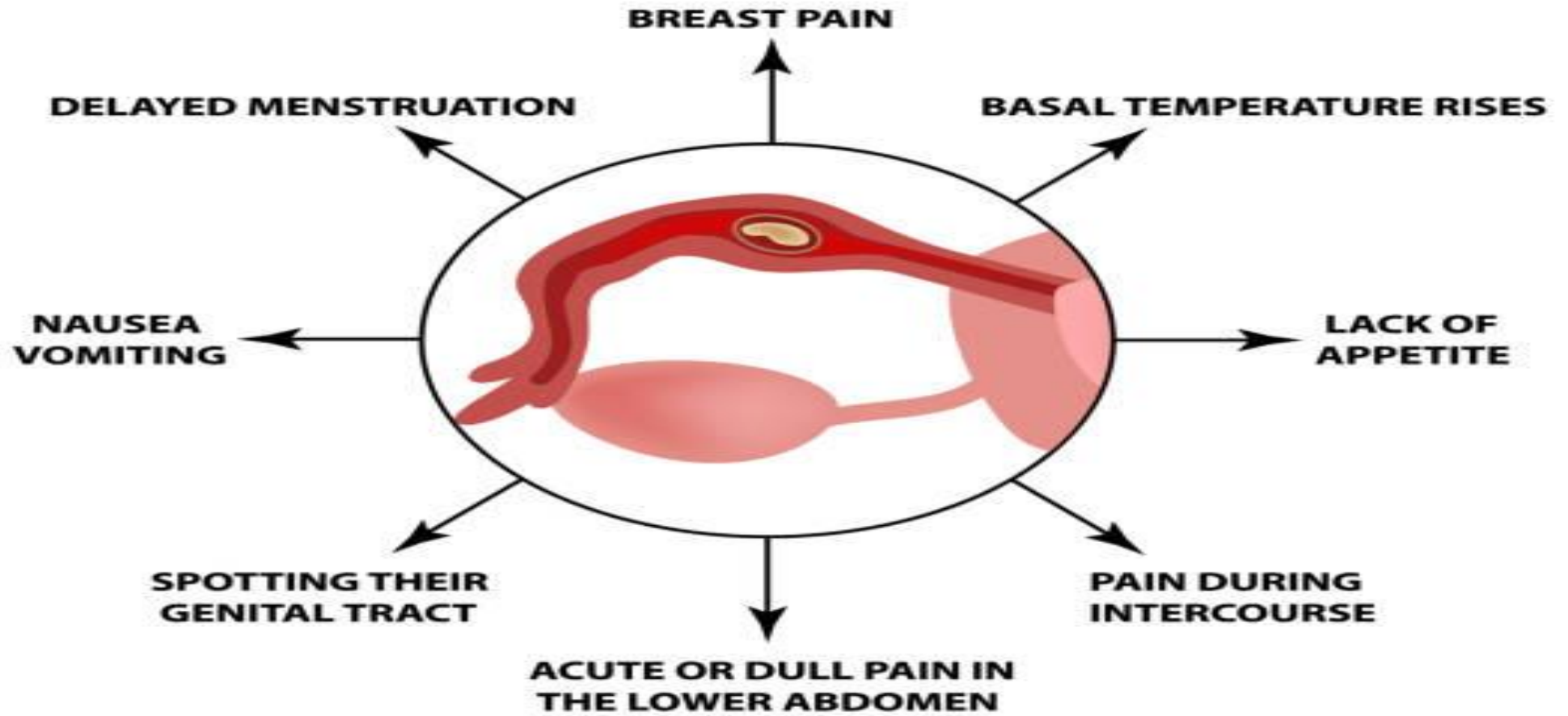
- An ectopic pregnancy is one in which the fertilized egg implants in tissue outside of the uterus and the placenta and fetus begin to develop there
- Put very simply, an ectopic pregnancy means "an out-of-place pregnancy"







SYMPTOMS OF ECTOPIC PREGNANCY



Positive pregnancy test in woman of reproductive age

• **Haemodynamically stable**
• No concerns of intraperitoneal bleeding

Assessment of history, risk factors, TV USS ± serum hCG

Tubal ectopic pregnancy diagnosed or suspected

• **Haemodynamic instability**
• Concerns of significant intraperitoneal bleeding

• Significant pain
• Adnexal mass >35 mm
• Fetal heart beat present
• Serum hCG >5000 IU/L

• No significant pain
• Adnexal mass <35 mm
• No visible fetal heart beat
• No intrauterine pregnancy
• Minimal free fluid

Urgent surgical management
Urgent escalation of care
Urgent volume replacement

• hCG 1500–5000 IU/L

• hCG <1500 IU/L
• Prefers medical management

• hCG <1000 IU/L
• Prefers expectant management

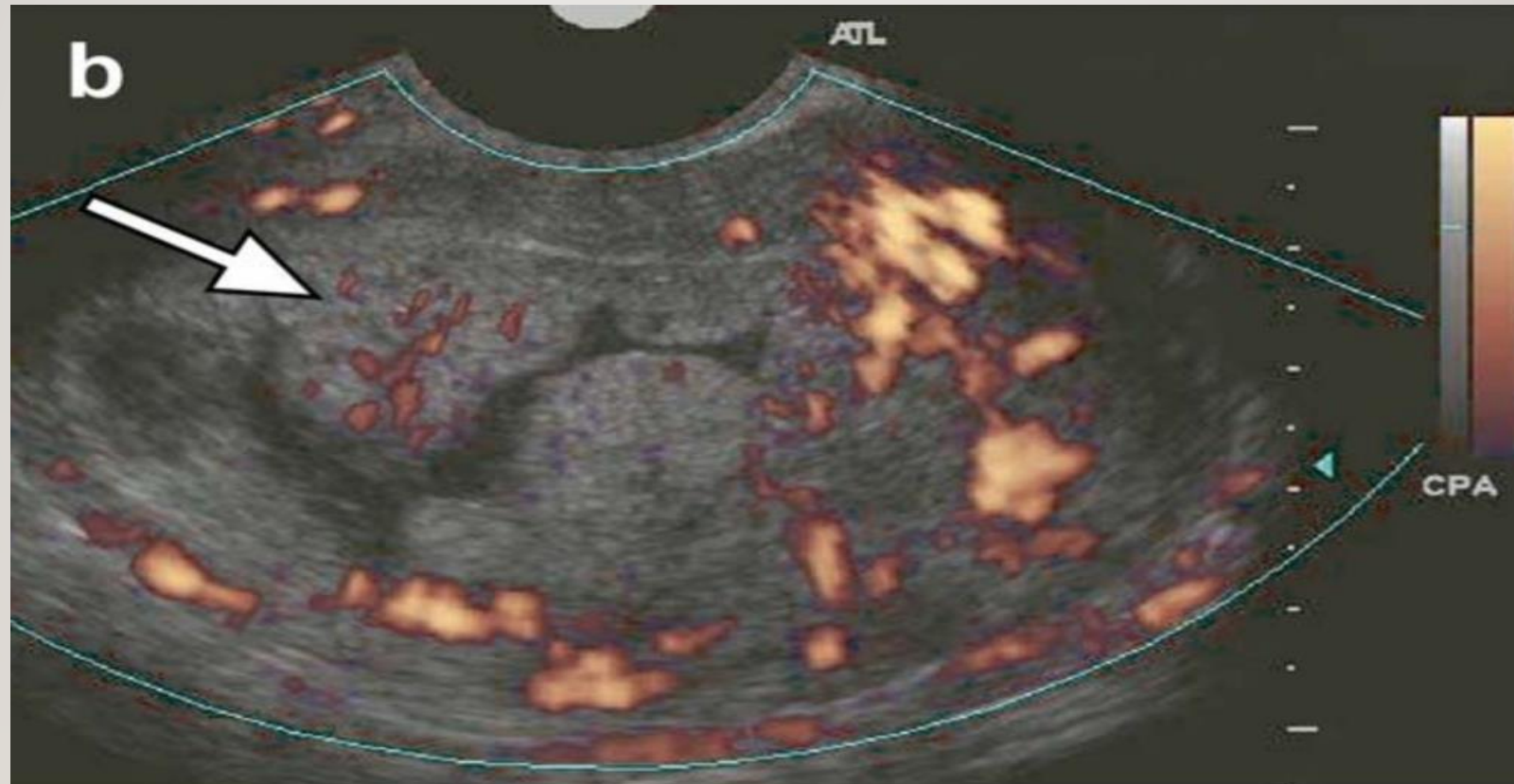
Surgical management

Medical management

Expectant management



MOLAR PREGNANCY



MOLAR PREGNANCY

- A molar pregnancy is an abnormal form of pregnancy in which a nonviable fertilized egg implants in the uterus and will fail to come to term. It is a gestational trophoblastic disease which grows into a mass in the uterus that has swollen chorionic villi-resembles grape.

Classifications

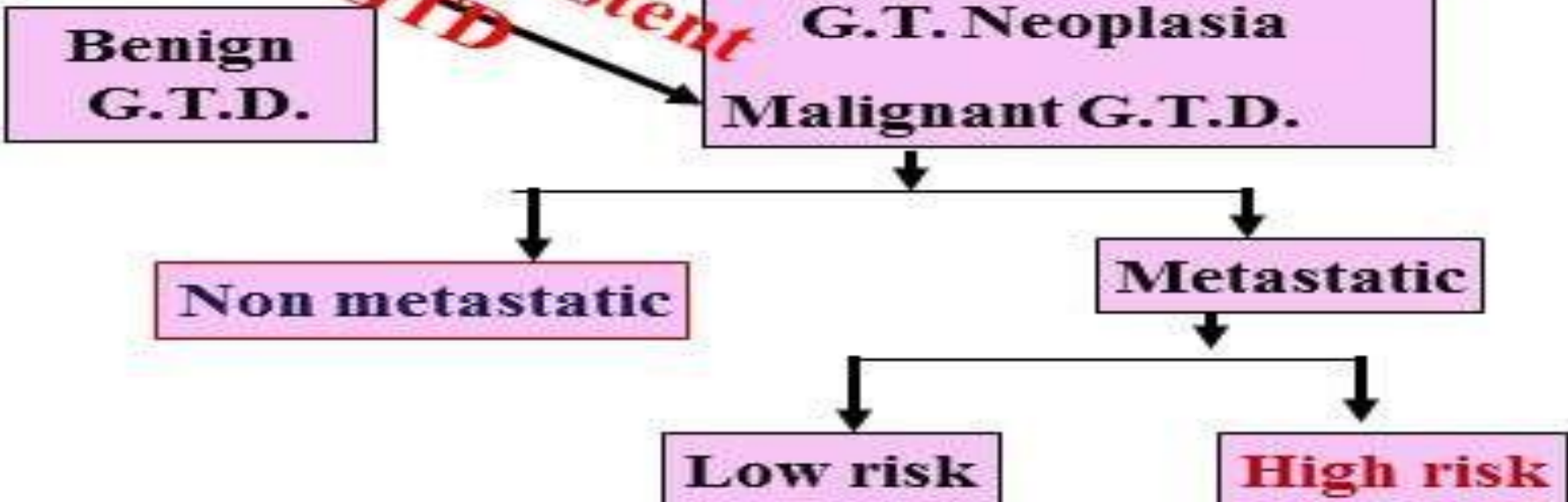
Gestational Trophoblastic Disease (GTD)

I-Pathologic Classification



II-Clinical Classification

**βhCG based:
WHO, FIGO,
ACOG 2004 &
RCOG 2010**



Molar pregnancy

Complete mole	Incomplete mole
Most common type of hydatidiform mole	
Diffuse thropoblastic hyperplasia, hydropic swelling of chorionic villi, no fetal tissue or membrane present	Hydropic villi and focal focal trophoblastic hyperplasia are associated with fetus or fetal parts
46XX or 46XY	Often triploid (XXY,XYY,XXX) with chromosome complement from both parents
2 sperm fertilize 1 empty egg or 1 sperms with reduplication	Single ovum fertilized with 2 sperms
15–20 % risk of progression to malignant sequale	

SPECTRUM OF GESTATIONAL TROPHOBLASTIC NEOPLASIA



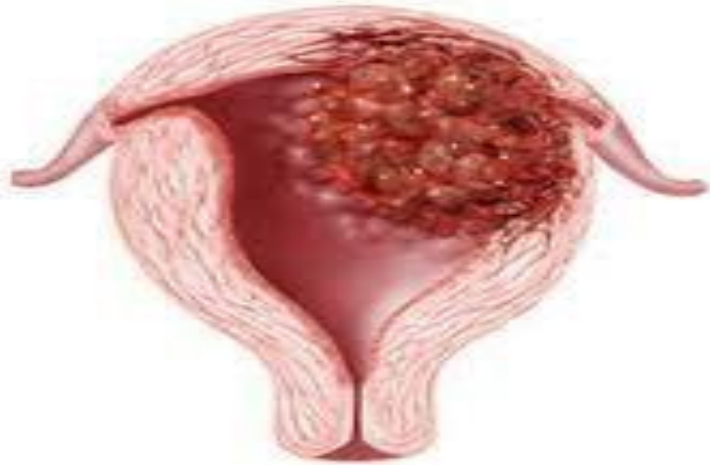
Complete hydatidiform mole



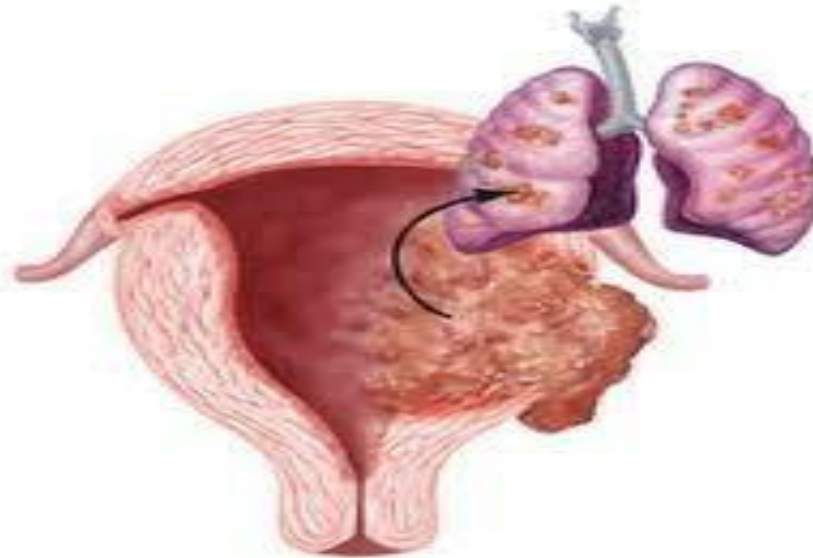
Partial hydatidiform mole



Coexistent mole and live fetus



Invasive mole



Choriocarcinoma



Placental site trophoblastic tumor

Symptoms & Signs of Molar Pregnancy



- **Passing grape-like clusters from the vagina**
- **Absence of fetal heartbeat**
- **Abdomen feels larger**
- **Severe nausea and vomiting**
- **Pelvic pain and discomfort**
- **Uterus unusually large for the stage of pregnancy**
- **High blood pressure**
- **Overactive thyroid gland**
- **Anemia**
- **Presence of ovarian cysts**

Table 1. Genetic and Histopathologic Features of Molar Pregnancy

	Complete	Partial
Karyotype	Generally diploid or tetraploid; generally all chromosomes paternal	Generally triploid; extra set of chromosomes is paternal
Hydropic villi	Diffuse	Focal
Trophoblastic hyperplasia	Diffuse	Focal
Scalloping of villi	Absent	Present
Fetal or embryonic tissue	Absent	Present
p57 expression	Negative	Positive

Clinical risk factors for molar pregnancy

Age (extremes of reproductive years)

<15

>40

Reproductive history

prior hydatidiform mole

prior spontaneous abortion

Diet

Vitamin A deficiency

Birthplace

Outside North America(occasionally has this disease)



Features Of Partial And Complete Hydatidiform Moles

Feature	Partial mole	Complete mole
Karyotype	Most commonly 69, XXX or - XXY	Most commonly 46, XX or -,XY
Pathology		
Fetus	Often present	Absent
Amnion, fetal RBC	Usually present	Absent
Villous edema	Variable, focal	Diffuse
Trophoblastic proliferation	Focal, slight-moderate	Diffuse, slight-severe
Clinical presentation		
Diagnosis	Missed abortion	Molar gestation
Uterine size	Small for dates	50% large for dates
Theca lutein cysts	Rare	25-30%
Medical complications	Rare	10-25%
Postmolar CTN	2.5-7.5%	6.8-20%





Gestational trophoblastic diseases
A range of pregnancy-related tumours commonly known as molar pregnancies.

Non-cancerous forms
Hydatidiform moles

Complete hydatidiform moles
(Androgenetic pregnancies)
Pregnancies formed from an egg with no chromosomes. The pregnancies contain no maternal DNA.

Partial hydatidiform moles
(Triploid gestations)
Two sperm fertilise a single egg. The pregnancies have too much paternal DNA.

Cancerous forms
Tumours or neoplasia

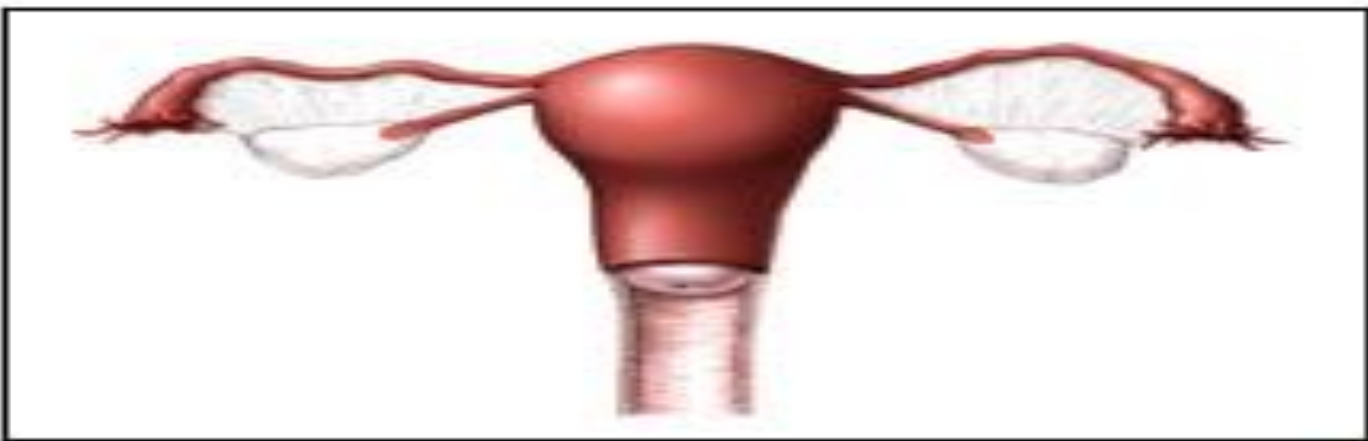
Invasive hydatidiform moles
Previously benign hydatidiform mole becomes malignant and moves to other sites in the body.

Choriocarcinoma
Very aggressive tumour occurring up to 15 years after the last pregnancy.

Placental site tumours
Tumour often occurring many years after the last pregnancy.

MANAGEMENT

- A molar pregnancy can't be continued as normal viable pregnancy
- 1. D & C-suction curettage.
- 2. Hysterectomy-when there is increased risk of GTN and there is no desire for pregnancy
- 3.HCG monitoring----repeat test till it is negative.



Normal uterus

**Early placenta
develops into
abnormal cysts**



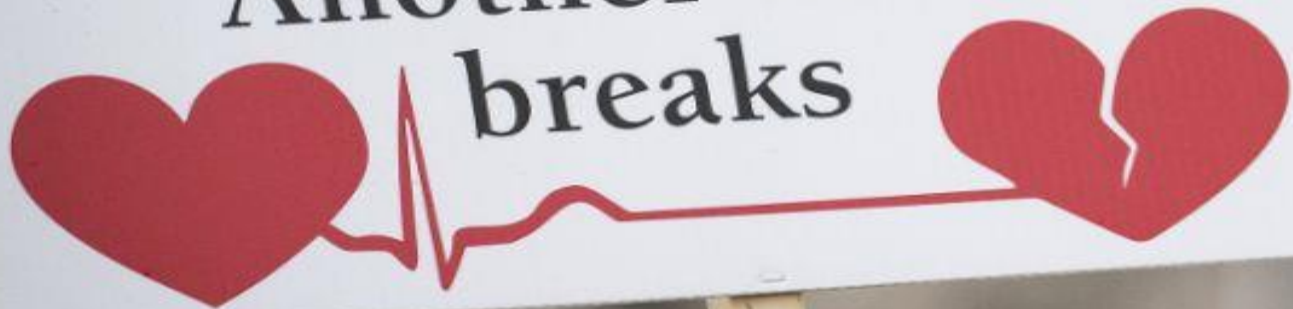
Uterus

Abortion



Abortion . . .

One heart stops
Another heart
breaks



25 MILLION UNSAFE ABORTIONS TAKE PLACE EACH YEAR WORLDWIDE



• This is nearly half of all abortions worldwide

• 1 out of 3 unsafe abortions occur in the worst conditions (untrained persons using dangerous methods)

**MOST UNSAFE ABORTIONS OCCUR IN
THE DEVELOPING WORLD**



Globally, 45 percent of abortions are unsafe.

Unsafe abortion accounts for 13 percent of maternal mortality worldwide.

Sources: Guttmacher and World Health Organisation

Abortion

- Loss of a pregnancy during the first 20 weeks of pregnancy, at a time that the fetus cannot survive.
- Such a loss may be involuntary (a "spontaneous" abortion), or it may be voluntary ("induced" or "elective" abortion).
- Miscarriage is the term used for spontaneous abortion, an unexpected 1st trimester pregnancy loss.

ABORTION

- 56 million abortions each year in world
- 45% -unhealthy
- >80% abortion occurs within 12 weeks.
- Induced
- Spontaneous –congenital abnormalities
 - -vascular disease
 - -diabetes , hormonal, infection, uterine abnormalities,
 - -accidental, intentional

What Causes Miscarriage?

- * The most common cause of miscarriage is a genetic abnormality.
- * Certain uterine abnormalities can cause miscarriage.
- * Often the cause of the miscarriage can't be determined at all.

**Everyone should be able
to access reproductive
healthcare without threat
of criminal prosecution
and intimidation.**

"Abortion is lowest where contraception and safe legal abortions are universally available – OBGYNs are urged to act as individual providers and through their FIGO member societies to protect women's health and rights. Simplified medical abortion provided by telemedicine services is a way to increase access to safe, acceptable and effective abortion care and provides women with increased autonomy."

Professor Kristina Gemzell Danielsson,
Chair, FIGO Committee for Human Rights, Refugees and Violence
Against Women



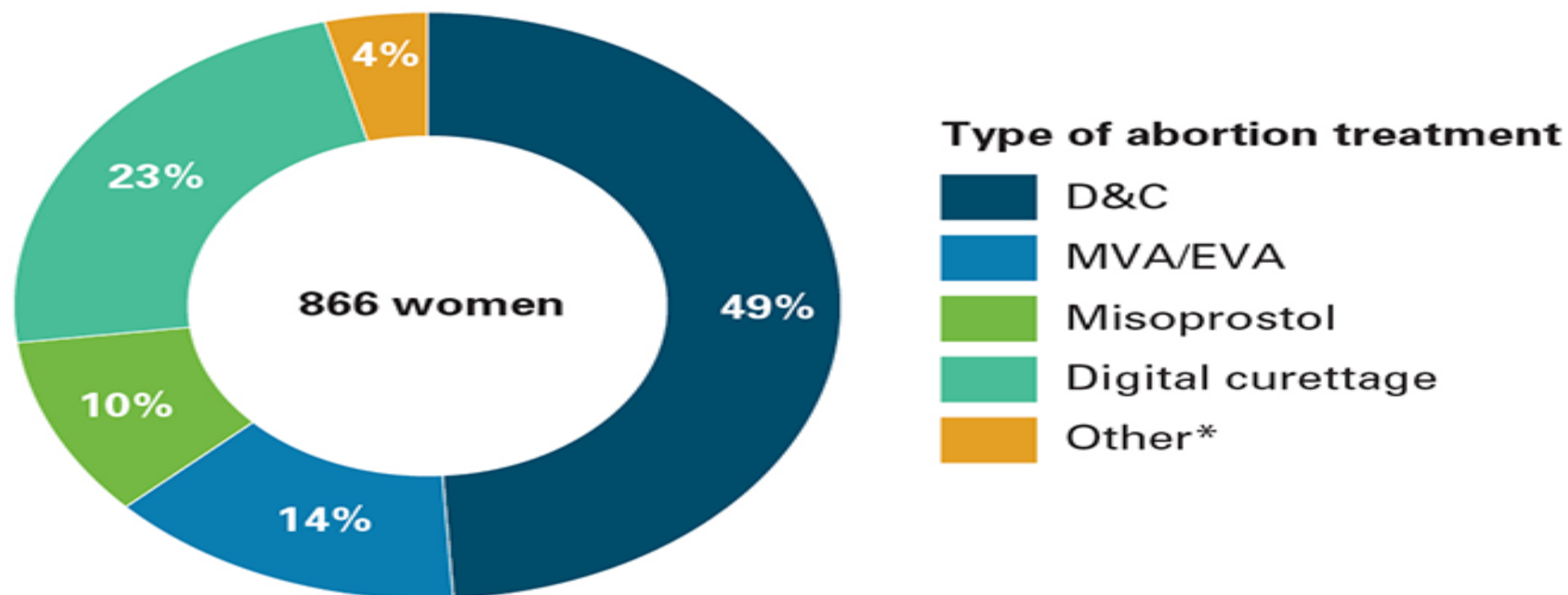
MANAGEMENT

- Medical
 - mifepristone+prostaglandin-safe
 - and effective-up to 10 weeks
 - Methotrexate + prostaglandin -
 - -up to 7 weeks.
- surgical
- MVA/D&C

MANAGEMENT

- American college of obstetrics and gynecology(ACOG)
- Protocol for medical management-
- Uterus <12 weeks-misoprostol 600 micro gm orally or
 - misoprostol 400 micro gm sublingually
- Every 3 times –total 3 doses
- 80% success.

3.4 Among women receiving postabortion care in Kinshasa, D&C is the most common form of treatment.



NOTES TO FIGURE 3.4

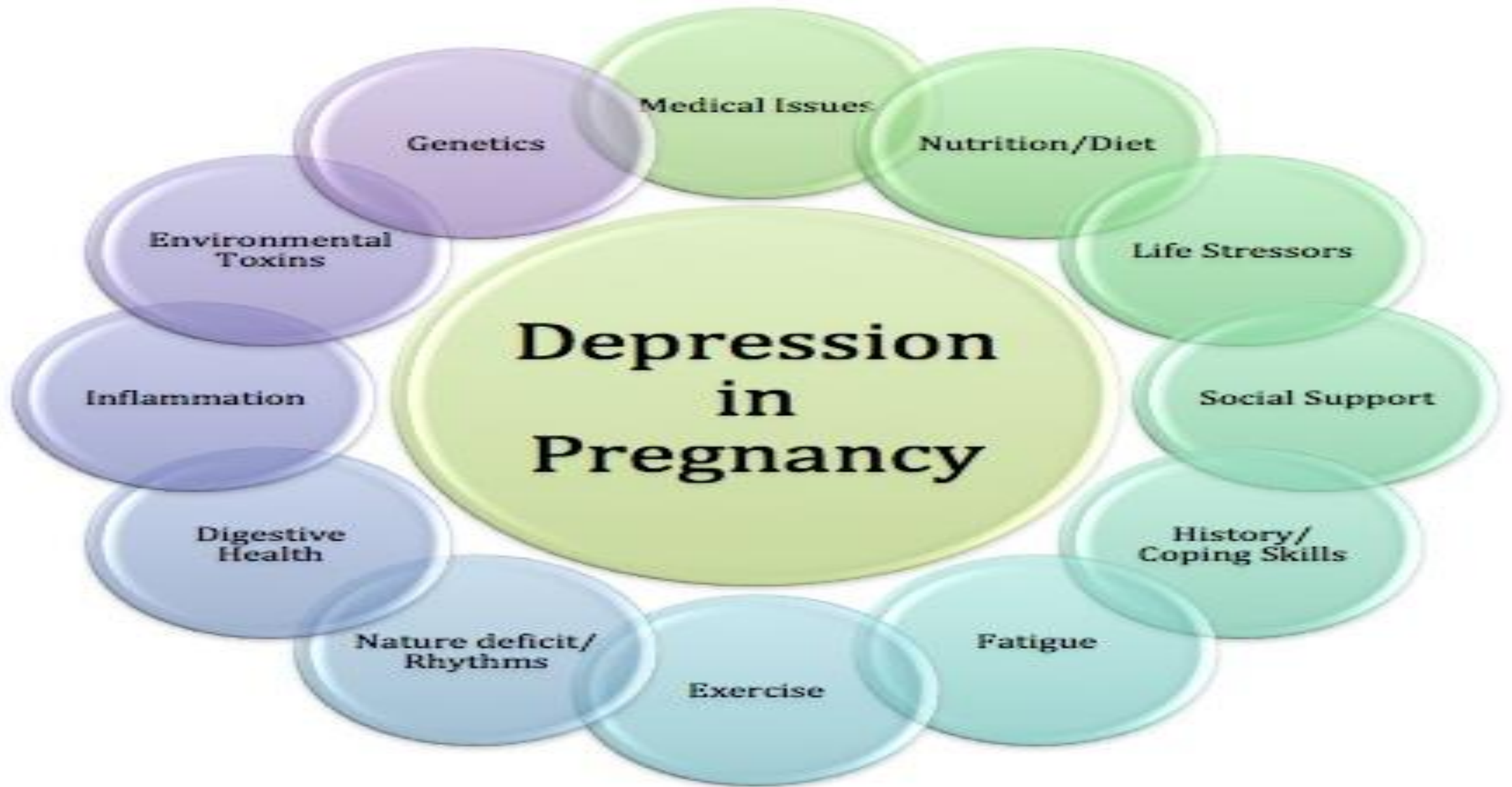
*Forceps evacuation or any other means.

Notes: Percentages calculated with weights. D&C=dilation and curettage. MVA=manual vacuum aspiration. EVA=electric vacuum aspiration.

Source: reference 6.

WHO

- Access to legal, safe and comprehensive abortion care including post abortion care is essential for the attainment of the highest possible level of sexual and reproductive health.



MANAGEMENT

- Managing all the causes.

OTHER CAUSES

- Hyperemesis gravidarum
- Implantation hemorrhage
- Ruptured corpus luteum cysts
- In most of the cases-counseling and symptomatic treatment is sufficient

Conclusions

- First trimester complications are common
- Family medicine doctors have the skills to manage the majority of these complications
- Misoprosol and MVA are excellent tools for primary care providers
- Psychological issues may be best managed by the primary care doctor



Healthy Foods

During The

First Trimester





Journey of Tocolysis

Dr. Milind R. Shah

MD, DGO, DFP, FICOG

President ISOPARB (2014-16)

Deputy Secretary General: FAOPS

Vice President of FOGSI (2011)

Managing Committee Member ISAR, IAGE, ISPAT

Chairman: Rural Obstetrics Committee (2004-08)

Peer reviewer for Journal of OBGYN of India

Prof. & HOD, Dept. of OBGYN, GNHMC, Solapur

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**WCPM, Punta Cana, Dominican Republic
4th June, 2022**



- * President ISOPARB (2016-18)
- * President, IMA (Indian Medical Association, Solapur Branch) (2021-22)
- * Founder President of IHRF (Infertility & High Risk Foundation)
- * Hon. Treasurer (FAOPS): Asia Oceania Federation of Perinatal Societies
- * Vice President of FOGSI (Federation of all Gynecological Societies of India) (2011)
- * Second Vice President, ISPAT (Indian Society of Prenatal Diagnosis & Fetal Therapy) (2019-21)
- * Deputy Secretary General InSARG (Indian Society of Aesthetic & Regenerative Gynecologists)
- * Ex-Chairman, Rural Obstetrics Committee of FOGSI (2004-2008)
- * Managing committee member-IAGE, ISAR, IFUMB, IMLEA
- * Peer reviewer for Journal of OBGY of India
- * Past Steering committee member-Asia Safe Abortion Partnership (ASAP)
- * Past President, Solapur OBGY Society (2001)
- * Prof. & HOD, Dept. of OBGY, Gandhi Natha H. Medical College
- * National Editor member for FOGSI Website
- * Visited many countries like **USA, UK, Canada, Chile, France, Switzerland, Japan, Thailand, Srilanka, Nepal, Pakistan, Afghanistan, Bangla Desh, Singapore, Malaysia, South Africa, China, Portugal, Vietnam, Taiwan, Indonesia, Mauritius, Philippines, UAE, Serbia, Peru, Brazil, South Korea & all over India** to deliver lectures on various topics in OBGY
- * Authored a book **"Hypertensive Disorders in Pregnancy"**, **"Pelvic Organ Prolapse"** and contributed more than 20 chapters in various books
- * Active Rotarian



“The problems are solved, not by giving new information, but by arranging what we have known since long”

— Ludwig Wittgenstein



One of the earliest descriptions of Preterm birth



- ★ *On December 25, 1642 when a widow gave birth prematurely to a male child, his mother Hannah Ayscough reportedly described that child as “so small that he could have been put into a quart mug” (≈ 1.3 liters)”*

The infant survived and grew up to be “Sir Isaac Newton.”

“However, a significant proportion of preterm births do not survive, let alone grow to become Newton.”

INTRODUCTION

According to WHO, 11.1% Of all livebirths worldwide are preterm.

Annually 4 million babies succumb to preterm birth

- Kinney MV, Lawn JE, Howson CP, Belizan J. 13 Million preterm births annually: what has changed this year? *Reprod Health*. 2012;9:28.

PRETERM BIRTHS: SCALE OF THE PROBLEM

EVERY YEAR

15 MILLION
BABIES ARE BORN TOO SOON

1 MILLION OF THESE
DIE FROM PRETERM BIRTH COMPLICATIONS

THAT'S

1 OUT OF EVERY 3 DEATHS
AMONG NEWBORN BABIES

Background: Indian Scenario- Preterm Birth

THE HINDU

[News](#) » [National](#)

India has the highest premature baby deaths: report

Special Correspondent

According to a report published recently, **India has the highest number of deaths due to premature births**, and ranks 36th in the list of pre-term births globally. The ranking included 199 countries.

Of the **27 million babies** born in India annually (2010 figure), **3.6 million are born prematurely**, of which **303,600 don't survive** due to complications.

Nearly half of all child mortality is due to pre-term births, a new report by Save the Children, titled 'Born Too Soon: The Global Action Report on Pre-term Birth' has revealed. The deaths due to pre-term births are second only to pneumonia, it notes.

In terms of deaths due to pre-term birth, India is at the top (indicating it fares the worst), while in terms of the rate of pre-term births, it is ranked 36th, after Malawi (ranked first), Pakistan (ranked eighth), Nepal (20th), and Bangladesh (24th), says the report.

Each year, 15 million babies, making up more than one in 10 births globally, are born too early, says the report. More than one million of those babies die shortly after birth; countless more suffer some type of lifelong physical, neurological, or educational disability, often at great cost to families.

Save the Children India Senior Advisor for Maternal, Child and Newborn Health Dr. Rajiv Tandon said: "The problem of premature birth needs both attention and intervention if India is to improve its maternal and child health record.

An estimated three quarters of the pre-term babies who die can survive without expensive care, if a few proven and inexpensive treatments and preventions are available globally, according to more than 100 experts who contributed to the report, representing almost 40 U.N. agencies, universities, and organisations.

The countries with the greatest numbers of preterm births are India – 3,519,100; China – 1,172,300; Nigeria – 773,600; Pakistan – 748,100; Indonesia – 675,700; United States – 517,400; Bangladesh – 424,100; Philippines – 348,900; Democratic Republic of the Congo – 341,400; and Brazil – 279,300.



Definition

Regular uterine contractions accompanied by progressive cervical dilation and/or effacement at less than 37 weeks gestation

20-50% of PTL diagnosis is incorrect



★ **Dilemma**

Interventions to stop preterm labor are not particularly effective – especially when not instituted early

★ **Solution**

Diagnosis based on some degree of uterine activity combined with a single cervical examination suggesting early dilatation or effacement



Diagnosis

- ★ Establish dates
- ★ History of contractions, risk factors
- ★ Abdominal exam for uterine activity
- ★ P/V examination – serial if reasonable
- ★ Sterile P/S examination alone should be done in PPRROM
- ★ Defer digital exam if there is undiagnosed vaginal bleeding until location of placenta is known

Harron et al



Establishing EDD - LMP

- ★ Naegele's rule can be used in conjunction with LMP if
 - First day of last menses is known
 - Period was normal
 - Cycle is regular and between 25-35 d
 - No recent hormonal contraception, lactation or pregnancy (3 subsequent spontaneous periods)



Establishing EDD - USG

- ★ Ultrasound should be used when LMP is unknown or criteria are not fulfilled for its use in calculating EDD
- ★ USG dating accuracy decreases as gestational age increases
 - 7-12 wks GA : +/- 5 days
 - 13-20 wks GA : +/- 1 week
 - 21-30 wks GA : +/- 2 weeks
 - > 30 wks GA : +/- 3 weeks
- ★ T, Y, V, U shapes on USG



Establishing EDD

- ★ Please tell someone the EDD
 - Inform woman of EDD from LMP if appropriate and reinforce at time of dating and/or 18 weeks USG
 - Document EDD on antenatal card
 - Document dates and findings of each USG on ANC card (include placental location)
- ★ Good dating is useless if no one but you knows EDD and if you are not available



Classification of preterm birth

- * Mildly preterm birth - **32 - 36 weeks**
- * Very preterm birth - **28 - 31 weeks**
- * Extremely preterm birth - **24 - 27 weeks**



Significance

- ★ Preterm birth accounts for 75% of perinatal mortality
- ★ Significant long term neonatal/pediatric sequelae
 - CNS and neurodevelopment
 - Respiratory
 - Blindness and deafness



Management – Four Objectives

- ★ Early Diagnosis
- ★ Identify and treat underlying cause if possible to prevent preterm labor
- ★ Attempt to stop labor when appropriate
- ★ Appropriate management of labor
- ★ Minimize neonatal morbidity and mortality



Preterm Labour

Warning signals :-

- ★ Low dull backache
- ★ Abdominal cramping – menstrual like cramps
- ★ Glairy mucous discharge
- ★ Feeling of pelvic pressure or heaviness in vagina



Principles of Management of Established PTL

- ★ Corticosteroids
- ★ Tocolysis
- ★ Antibiotics
- ★ Careful intrapartum monitoring
- ★ Vaginal delivery is preferred
- ★ Transfer in utero



Prolongation of Pregnancy

- ★ Less than 40% (10-20%) of patients in preterm labor will be candidates for tocolysis
- ★ Goal of tocolytic therapy
 - Gain 48 hours for corticosteroids
 - Gain transport time
 - Gain time to optimize personnel



Contraindications for Tocolysis

- ✦ Continuing pregnancy is not advised like severe PIH, chorioamnionitis, IUD
- ✦ Specific tocolytic agents are contraindicated
- ✦ If labor is advanced



Tocolytics (Uterine Relaxants)

Gr. *tokos*: childbirth, *lytic*: capable of dissolving



- * Specifically developed to be uterospecific
 - Oxytocin receptor antagonist – Atosiban
- * Not specifically developed (Not uterospecific)
 - Beta-agonists
 - NO donors
 - NSAIDs
 - CCBs
 - MgSO₄

Tocolytics – No strong evidence for efficacy

- ★ Fluid bolus: Small trial (n=48), no detected effect
- ★ Ethanol: Small trials, no benefit over placebo, ritodrine more effective, concern about side effects
- ★ Sedation: No evidence, concern about side effects
- ★ Magnesium Sulphate: Small trials, no benefit



Tocolytics – Strong evidence for efficacy

- ★ Beta sympathomimetics (Ritodrine, Isoxsuprine)
 - Highly effective for delaying delivery in short term, no demonstrated effect on neonatal outcome
- ★ PG Synthetase inhibitors (Indomethacin, mefenamic acid)
 - More effective than placebo in delaying delivery > 48 hrs and beyond
- ★ Calcium channel blockers (Nifedipine)
- ★ Terbutalin – asthmatic patients
- ★ Nitroglycerine dermal patch
- ★ Oxytocin antagonists – Atosiban
- ★ Progesterone



Tocolysis

Betamimetics :-

- ★ They are the most commonly used drugs for tocolysis.
- ★ Beta 2 receptors are present in myometrium, blood vessels & bronchioles.

Ritodrine

- ★ It was the only drug approved by US FDA for tocolysis
- ★ Withdrawn voluntarily by manufacturer in USA since 2003 due to report of pulmonary edema with IV use but used in other countries.



Doses

- ★ Isoxuprine: IV, IM, Oral
0.2-1 mg/min for 10 min. followed by
0.1-0.3 mg/min, followed by oral 10-20
mg TID
- ★ Ritodrine: IV, Oral
100 mcg/min, increase every 10 min.
by 50 mcg followed by 20 mg TID



Tocolysis

Magnesium Sulphate

- ★ Useful in PIH , diabetes & hyperthyroidism where beta mimetics are contraindicated.
- ★ 4 gm loading dose in 100ml over 20 min. Followed by 2 gm/hr is given.
- ★ Reported success rate varies between 64 to 91 percent.
- ★ Monitoring for toxicity is done by knee jerk, urine output & respiration



Tocolysis

Indomethacin

- ★ **PG synthase inhibitor 50 – 100 mg orally followed by 25-50 mg 4 to 6 hrly**
- ★ **It is useful in polyhydramnios as it decreases the liquor also**
- ★ **It increases neonatal morbidity by causing premature closure of ductus , may cause renal damage & necrotizing enterocolitis.**



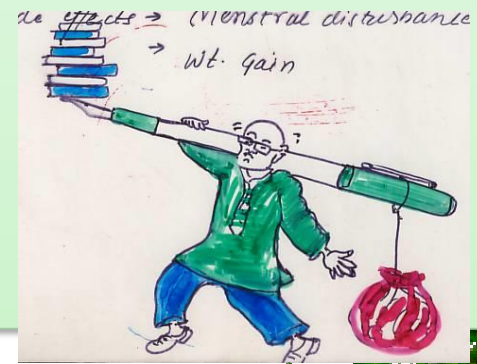
Choice of Tocolytics

★ Licensed preparations

- Oxytocin receptor antagonist – Atosiban
- Beta agonist – Ritodrine, isoxsuprine, Terbutaline, salbutamol, fenoterol

★ Unlicensed preparations/not approved by regulatory authority

- Calcium channel blockers [CCBs] - Nifedipine, Nicardipine
- Nitric oxide donors (No donors)- glyceryl trinitrate [GTN]
- PG synthetase inhibitors – Indomethacin, sulindac,
COX-2 inhibitors
- MgSO₄ (magnesium sulfate)



Atosiban



Royal College of Obstetricians
and Gynaecologists
Setting standards to improve women's health

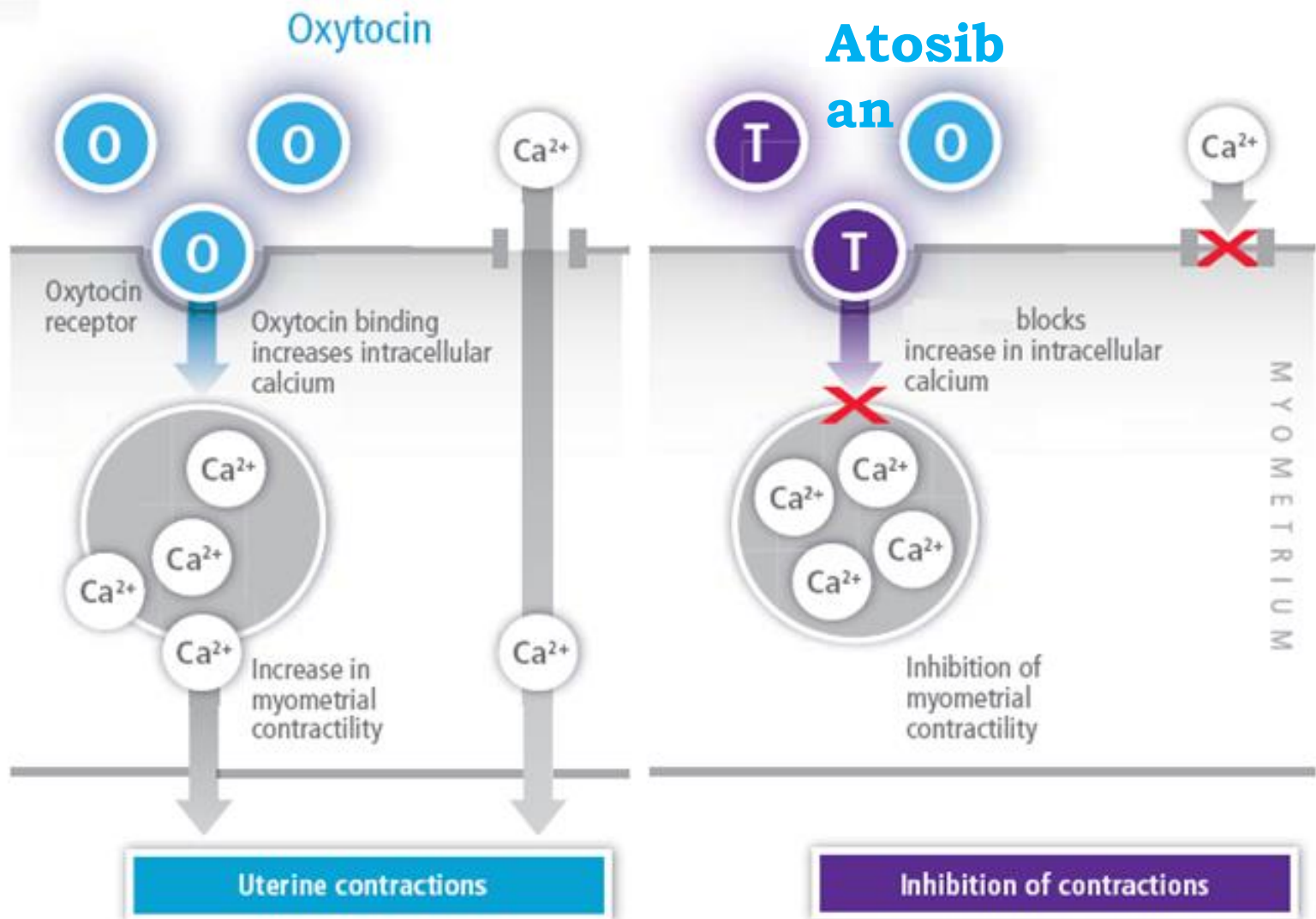


Recommended
**atosiban as first line
agent in the
management of
Preterm labor . [2,3]**

Atosiban should be considered a **first-
line tocolytic** for the management of
Spontaneous Preterm Labor. [1]

1. **Guidelines for the management of spontaneous preterm labor.** *J Perinat Med.* 2006;34(5):359-66.
2. RcoG. Tocolytic drugs for women in preterm labour: Royal College of Obstetricians and Gynaecologists (RCOG). 2002.
3. [Expert Opin Pharmacother.](#) 2014 Apr;15(6):787-97.

Mechanism of action of Atosiban



A competitive antagonist of human oxytocin receptor

Therapeutic Indications



- ★ Indicated to delay imminent pre-term birth in pregnant adult women with:
 - Regular uterine contractions of at least 30 seconds duration at a rate of ≥ 4 per 30 minutes
 - Cervical dilation of 1 to 3 cm (0-3 for nulliparas) and effacement of $\geq 50\%$.
 - Gestational age from 24 until 33 completed weeks
 - Normal foetal heart rate

Dosage & Administration



Step I – 'Initial bolus i.v. injection'
0.9ml of **ATOSIBAN** SOLUTION FOR INJECTION (7.5mg/ml).



Step II – 'Loading infusion'
Continuous infusion of **Atosiban** CONCENTRATE FOR SOLUTION FOR INFUSION. (37.5 mg/5 ml)

Infusion rate of 24ml/hour = 300µg/min for 3 hours.

Withdraw 10ml solution from a 100ml infusion bag and discard. Replace it with (2 x 5ml vials)



iv to pregnant woman

Step III – 'Subsequent infusion'
Follow by a lower dose of **Atosiban**

CONCENTRATE FOR SOLUTION FOR INFUSION. (37.5 mg/5 ml)

Reduced infusion rate of 8ml/hour = 100µg/min for up to 45 hours.

Prepare a new 100ml bag by withdrawing 10ml solution from a 100ml infusion bag and discard. Replace it with (2 x 5ml vials) **Atosiban**



iv to pregnant woman

Standard Dosing Regimen for Atosiban



Administered Intravenously in Three Successive Stages

Step	Regimen	Dose	Infusion rate	Duration
1	0.9 ml I.V. injection	6.75 mg	Bolus	Given over 1 minute
2	I.V. loading infusion	54 mg /3 hrs (18mg/hr)	24 ml/hr (300µg/min)	3 hr
3	I.V. infusion.	Up to 270 mg (6 mg/hr)	8ml/hr (100 µg/min)	Up to 45 hours

The total dose should not exceed **330.75 mg**

Contraindications

- Gestational age : < 24 or > 33 completed wks.
- PROM >30 wks of gestation
- Abnormal foetal heart rate
- Antepartum uterine hemorrhage
- Eclampsia & severe pre-eclampsia

- Intrauterine foetal death
- Suspected intrauterine infection
(chorioamnionitis)
- Placenta praevia, Abruption placenta
- Any other conditions of the mother or foetus, in which continuation of pregnancy is hazardous
- Hypersensitivity to the atosiban or excipients

Adverse Reactions



- ADRs were generally of a mild severity.
- The most commonly reported adverse reaction in the mother is **Nausea** (11 %).
- No specific ADR in newborn.

Di Renzo GC, Roura LC; European Association of Perinatal Medicine-Study Group on Preterm Birth. Guidelines for the management of spontaneous preterm labor. J Perinat Med. 2006; 34(5):359-66.

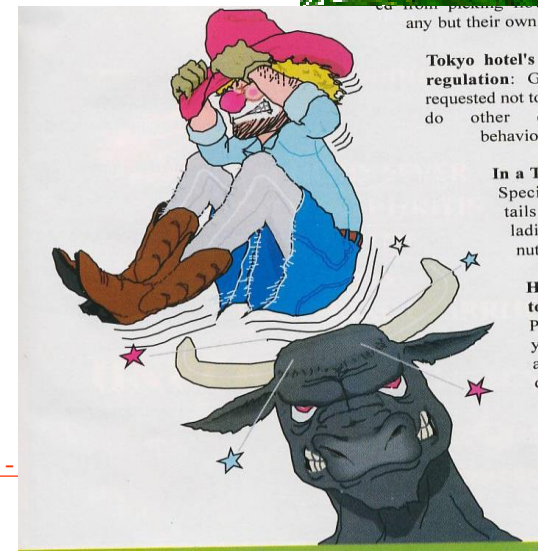
[Tractocile International prescribing information.](#)

<http://www.medicines.org.uk/emc/medicine/4305/SPC/Tractocile+7.5+mg+ml+Concentrate+for+Solution+for+Infusion/>

Atosiban Safety - assessment of placental & fetal circulation

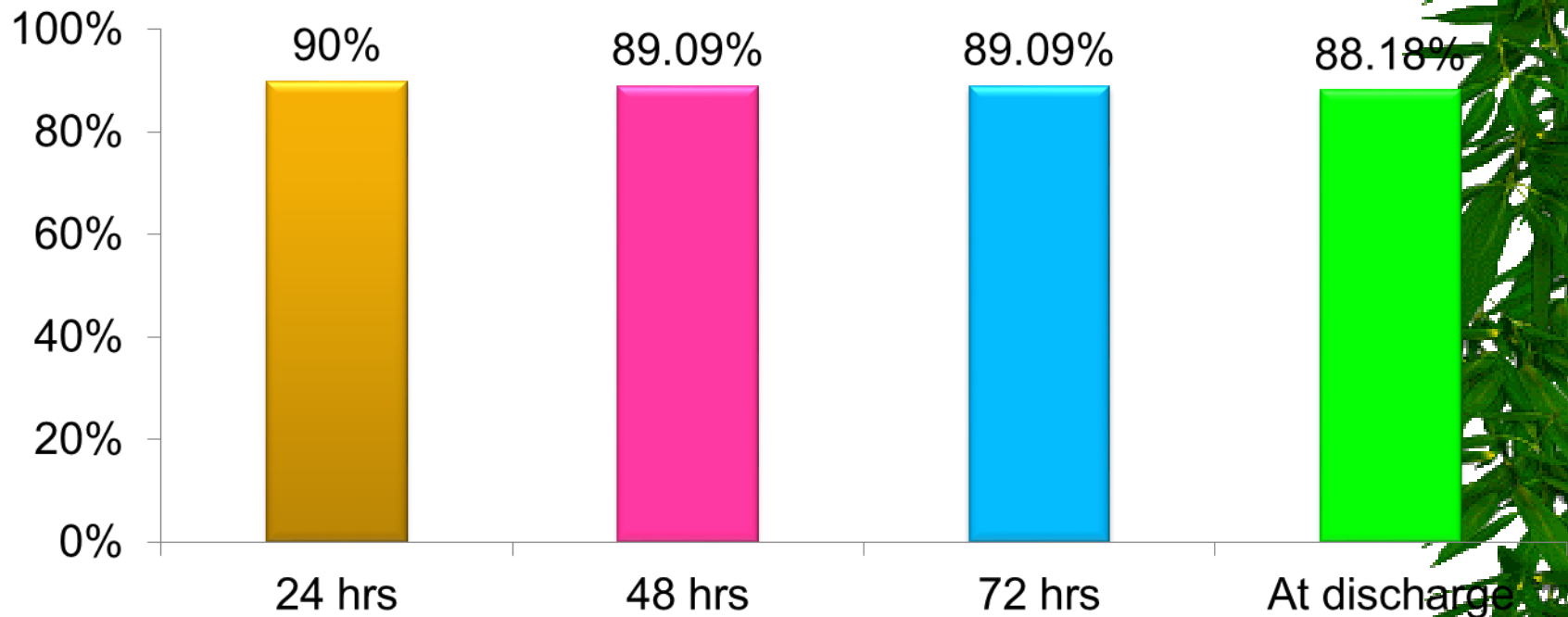
- **Atosiban** doesn't alter uterine nor fetal arterial blood flow pattern.
- Hemodynamic cardiac activity in fetuses remains unaffected.

[Grzesiak M, Wilczynski J. Preliminary report of 48-hours Atosiban administration in spontaneous preterm labor - placental and fetal circulation. Neuro Endocrinol Lett. 2013;34\(7\):681-6.](#)



Out of 110 patients, 98 patients (89.09%) remained undelivered up to 72 hrs after completion treatment. Ninety seven patients (88.18%) remained undelivered till the end of their hospital stay (≤ 7 days).

Percentage of Undelivered patients till discharge



No alternative tocolytics were required during the entire study

No retreatment with Atosiban was required during the entire study

No cases of AEs reported or observed during the entire study

No SAEs or deaths reported

All patients tolerated Atosiban well

Side effects of Beta sympathomimetics

- ★ Tachycardia - maternal and/or fetal
- ★ Headache and nasal congestion
- ★ Hyperglycemia / Hypokalemia
- ★ Hypotension
- ★ Pulmonary edema – Multiple gestation, other interventions, infection
- ★ Myocardial ischemia



Contraindications to Beta sympathomimetics

- ★ Maternal cardiac disease – structural, ischemic, rhythm
- ★ Significant APH
- ★ Poorly controlled medical disorder like Type I DM, hyperthyroidism, severe anemia
- ★ Contraindications to prolongation of pregnancy like PIH, chorioamnionitis, suspected fetal compromise



ATOSIBAN VS. β Receptor Agonist

- ❖ **β -Agonists are not uterospecific** and hence have multiorgan side effects.
- ❖ Atosiban have superior efficacy **without the conventional cardiovascular side effects** compared to **β -agonist**.
- ❖ **β -Agonists are gradually being phased out** of use because of less efficacy and higher rate of maternal adverse drug reaction.
- ❖ **Atosiban** is very useful in patients **with heart disease and multi-fetal pregnancies (twins)**, anemia where **β -agonist are contraindicated**.





- β –agonists use is decreasing worldwide due to safer alternative **Atosiban.**
- Atosiban is as effective as nifedipine with fewer cardiovascular side effects.
- Nifedipine (oral) : **rapid onset preparations compromise safety** and **slow-release preparations compromise efficacy.** [fetomaternal adverse effects]
- The **high quality evidence base** & serious concerns about the safety of other agents : **Guidelines recommend atosiban as first-line therapy** for the treatment of spontaneous preterm labor.

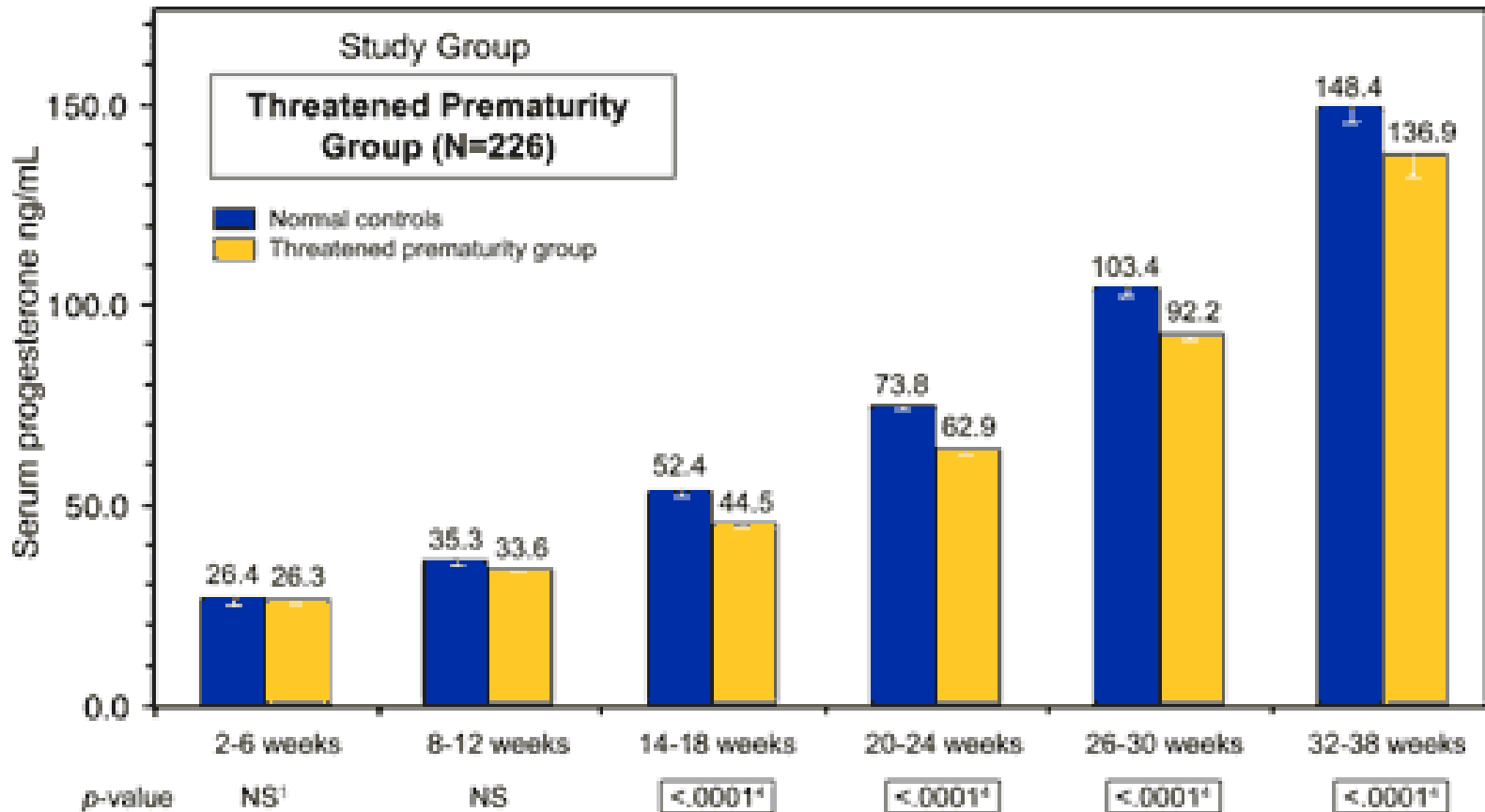
Minimizing Neonatal Adverse Outcomes

- ★ Respiratory distress syndrome (RDS) is a major concern – Incidence is reduced due to newer therapies
- ★ RDS plays a role in several other conditions
 - Intraventricular hemorrhage (IVH)
 - Necrotising enterocolitis (NEC)
 - Persistent pulmonary hypertension (PPHN)
 - Other respiratory conditions



Progesterone Levels Normal vs. Threatened

Comparison of Progesterone Levels
Means of All Levels at Six-week Intervals



1. Not statistically significant
2. F-test (equal variance)
3. F-test (unequal variance)
4. Mann-Whitney U test

Mean Progesterone – Six-week intervals

Progesterone: Side Effects and Precautions

Precautions

- Discontinue if thrombosis or thromboembolism occurs
- Consider discontinuing if allergic reactions occur
- Decreased glucose tolerance: Monitor pre-diabetic and diabetic women
- Fluid retention: Monitor women with conditions that may be affected by fluid retention, such as preeclampsia, epilepsy, cardiac or renal dysfunction
- Depression: Monitor women with a history of clinical depression; discontinue if depression recurs

Makena™ Prescribing Information, Ther-Rx Corporation St. Louis, MO February, 2011



Progesterone vs. Cerclage

Current recommendations...

* Short cervix who have NO previous preterm birth → Vaginal progesterone

* Previous preterm birth. → 17- alpha hydroxyprogesterone

* For women with a previous preterm birth AND a short cervix. → Cervical cerclage

* Supplemental cerclage for short cervix and NO previous preterm birth? → NO DATA

Am J Obstet Gynecol 2012;206:376-86

ACOG practice bulletin no. 130: Obstet Gynecol. 2012;120:964-73



Genetic

- ★ Important component of idiopathic group.
 - Single gene polymorphisms of cytokines in both mother and fetus may be responsible
 - Polymorphisms involving $\text{TNF}\alpha$ -308, IL-1 β and IL-6 have been most consistently associated with spontaneous preterm labour and preterm birth.



Important

- ★ Uterus is the best incubator at no extra cost. Uterus is the best transporter also.
- ★ Short term tocolysis is proved beyond doubt, it gives time for steroids to work .
- ★ Long term tocolysis is not supported by evidence based medicine, still it is widely practiced.



Thank You



LOW COST INTERVENTIONS TO IMPROVE OUTCOMES IN NEWBORNS.

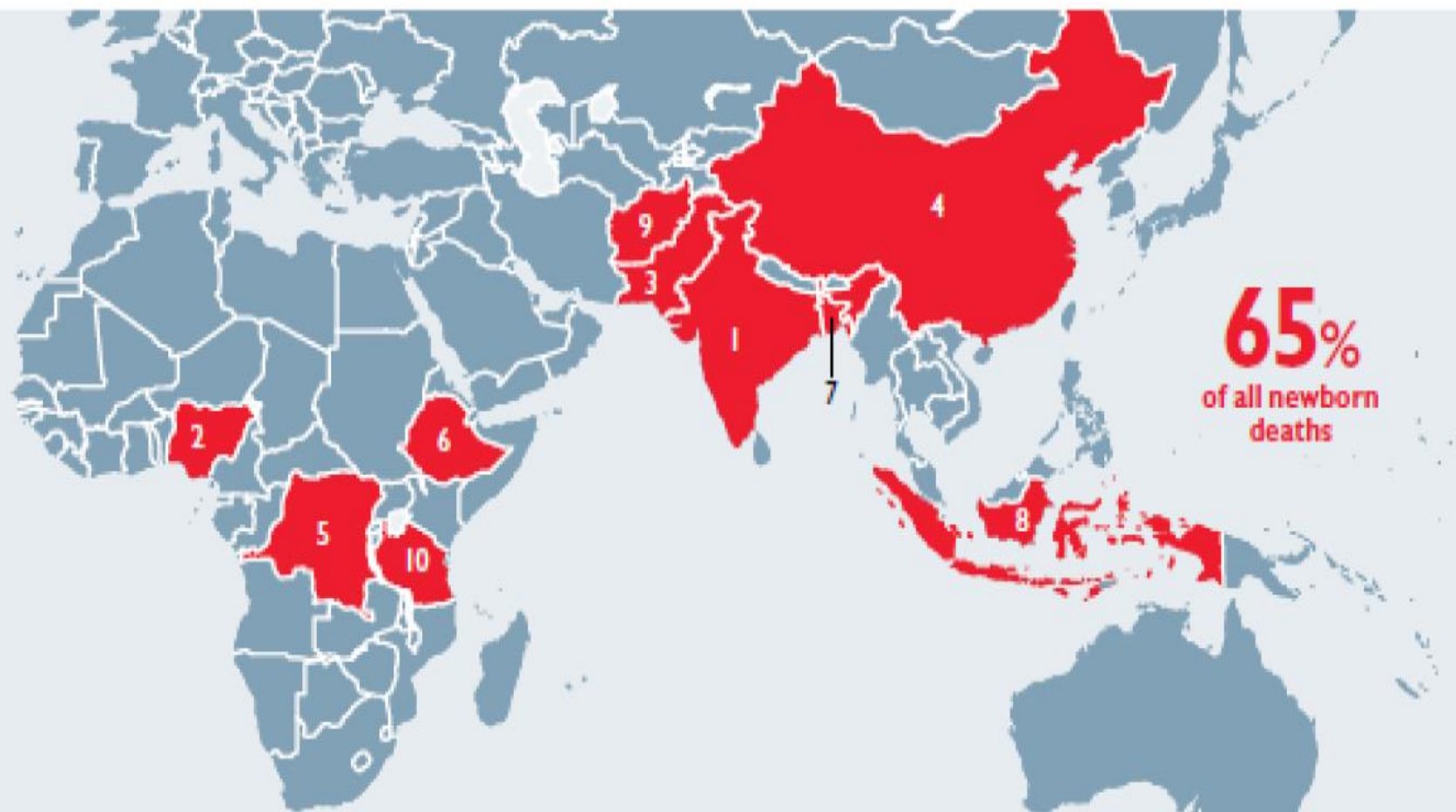
Ranjan Kumar Pejaver.

FRCPI,FRCPCH (UK),FIAP,FNNF.

**Chief Neonatologist,
People tree @Meenakshi Hospitals.**

President elect NNF India

MOST NEWBORN DEATHS OCCUR IN JUST 10 COUNTRIES



1	2	3	4	5	6	7	8	9	10
India	Nigeria	Pakistan	China	DR Congo	Ethiopia	Bangladesh	Indonesia	Afghanistan	Tanzania
876,200	254,100	169,400	143,400	137,100	81,700	79,700	66,300	51,000	48,100

1,907,000 deaths out of 3,100,000



Burden of Neonatal health problems

- ▣ Each year 19% of the world's infants, awesome 25 million are born in India.

Neonatal mortality rate (NMR)- 23/1000 live births

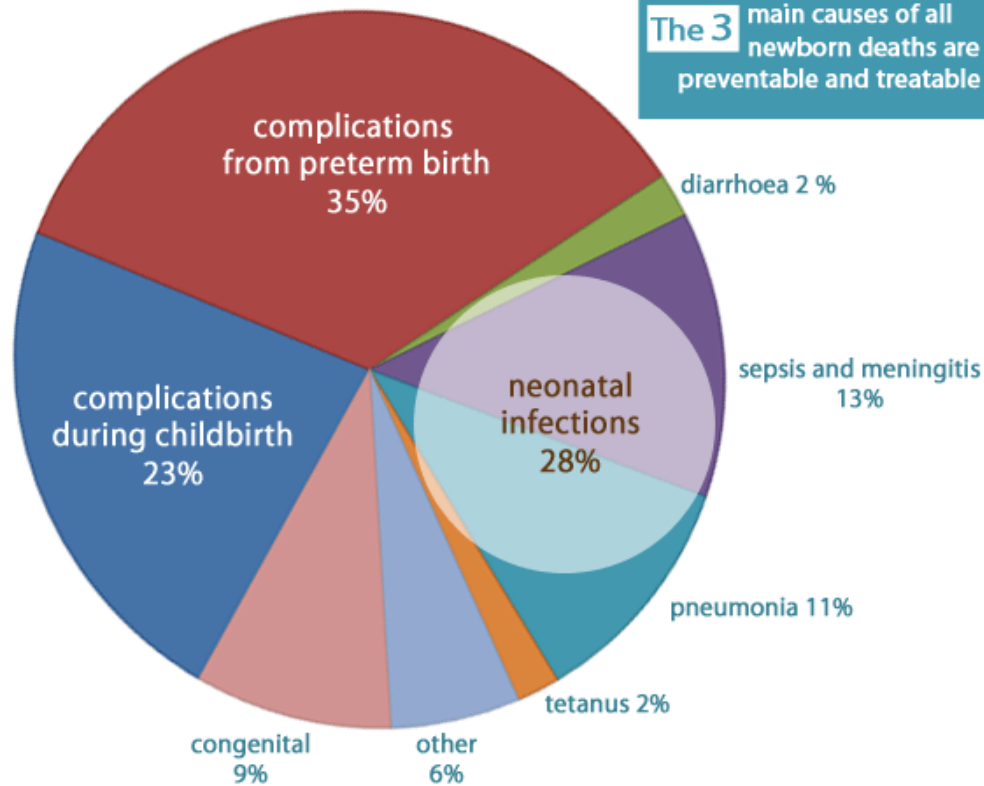
Early NMR – 19 and late -4

- ▣ Infant mortality (IMR)– 39/1000 live births.
- ▣ Under 5 mortality rate – 47/1000 live births

- ▣ Neonatal mortality constitutes 2/3 of IMR
- ▣ Constitutes nearly 1/2 of under 5 mortality
- ▣ **Goal is to reduce NMR to less than 10 by 2030**

Causes of neonatal mortality

Liu et al. Lancet 2012



Source: Liu L, Johnson H, Cousens S et al. 2012. Global, regional and national causes of child mortality: an updated systematic analysis. Lancet 379(9832):2151-61.

Cost effective interventions to improve outcomes in the preterm newborn

1. Antenatal steroids for women in preterm labor
2. Magnesium sulphate in preterm labor
3. Delayed/deffered umbilical cord clamping
4. Resuscitation: regulating oxygen
5. Temperature control in the DR
6. Kangaroo mother care
7. CPAP vs ventilator
8. Breast feeding
9. Early feeding vs TPN
10. Antibiotics when needed

Antenatal Corticosteroids for prevention of RDS in preterm infants

Single course of antenatal steroids:

21 trials , 4038 infants

- ↓ RDS RR 0.66; (95% CI 0.56 -0.77)
- ↓ Need for respiratory support and NICU admission
- ↓ IVH RR 0.55 (95% CI).44 -0.76)
- ↓ NEC RR 0.50 (95% CI 0.32 – 0.78)
- ↓ Neonataldeaths RR 0.69(95% CI 0.59-0.81)
- Standard of care for women at risk of preterm birth before 32 weeks GA.

- **World Health Organization & United nations**

- UN Commission on life saving commodities for women and children

- ‘ ..estimated that up to 400 000 lives could be saved each year by antenatal corticosteroids in low resource settings’

- **Low-Middle income countries:**

- Coverage of antenatal corticosteroids for all deliveries between 28 to 34 weeks of gestation is Overall is 52%.

Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Doyle LW et al. Cochrane Database Syst rev 2009

In 5 trials, 6145 infants:

Antenatal magnesium sulphate therapy given to women at risk of preterm birth:

↓ risk of cerebral palsy
(RR 0.68; 95%CI 0.54 - 0.87)



Antenatal magnesium sulphate for neuroprotection of

To reduce incidence motor disability & cerebral palsy(30%) neonates.*Doyle LW et al. Cochrane Database Syst rev 2009*

Mag sulph regulate excitatory stimuli by blocking NMDA receptors.

Vasoactive properties improve cerebral blood flow.

Prevents neuronal injury from proinflammatory cytokines

May have an anti apoptic effect

Monitoring- resp rate, patellar reflexes.

NNT at 34 weeks is 56, and at less than 30 weeks is 46

Australian Clinical Practice Guidelines for antenatal magnesium sulphate for neuroprotection of the fetus, infant and child

In women at risk of early preterm imminent birth, use magnesium sulphate for neuroprotection of the fetus, infant and child

- When GA is < 30 weeks (in Canada <32 weeks)
- When birth is planned or expected within 24 hrs
- Regardless of plurality
- Regardless of the reason women are considered to be at risk for preterm birth
- Regardless of parity
- Regardless of anticipated mode of birth
- **Whether or not antenatal steroids have been given**
- **IV 4g loading dose over 20- 30 min, then 1g per hr maintenance until delivery or for 24 hrs, whichever comes first**

Cord clamping at birth:

Traditionally what happened?

Active management of 3rd stage:

- giving an uterotonic medication**
- Clamping and cutting the cord.**
- delivery of the placenta.**

Thought to reduce PPH.

non -interventionalistic approach.

Approx. 75% of blood available for placental to fetal transfusion is transfused in the first minute.

Potential benefits:

decrease in neonatal /infant anemia.
Less fetomaternal transfusion from fetal blood in placental vessels.

Possible harm:

Higher rate of Polycythemia and
higher levels of neonatal jaundice
Increases maternal blood loss.

Meta- analysis: 10 studies: 454 preterm infants <37 weeks,

**delayed cord clamping: > 30 seconds
vs immediate cord clamping:< 20 seconds**

Rabe et al Neonatology 2008

↑ Hematocrit at birth or 1 hr of age (p= 0.0007)

↓ Transfusions for anemia (p= 0.005)

↓ Number of transfusions (p= 0.0004)

↓ Intraventricular hemorrhage (p= 0.002)

↓ Late onset sepsis in 1 study (Mercer et al) 3% vs 22%)

DCC in developing countries:

DCC is safe & inexpensive way to prevent infant anemia.

Higher iron stores –beneficial to infants & mothers with low ferritin levels.

Exclusively breast fed infants,

low birth weight infants

In countries where severe anemia of mother & newborn is common,

blood transfusions are not readily

available, DCC should be helpful.

Umbilical Cord Milking

Hosono S et al. Arch Dis Child Fetal Neonatal Ed 2008

- 40 preterm infants: 24-28 weeks
- immediate cord clamping (20) vs umbilical cord milking (20)
- 20 cms, 2-3 times

Increased initial Hb ,higher BP at admission

Decreased need for transfusion.

Decreased days of ventilation.

Decreased oxygen days.

No difference in IVH

No difference maximum bilirubin.

Use less oxygen for resuscitation

100% oxygen versus Room Air

Three meta-analyses studies published

first breath and cry of newborns resuscitated with 100% oxygen was significantly delayed compared with those resuscitated with room air (mean difference, 1.5 min [2.02 to 0.98]).

Short-term neurologic outcomes appear comparable

A disconcerting observation is the evidence of prolonged persistence of oxidative stress in infants resuscitated with 100% oxygen.

2017 NRP Major Changes



Oxygen Use:

- **Infants \geq 35 weeks gestation** begin with 21% oxygen (room air).
- **Infants $<$ 35 weeks gestation** resuscitation should begin w/ 21%-30% FiO₂ to maintain appropriate target preductal oxygen saturations. (Class I, LOE B-R)
- Initiating resuscitation w/ higher than 65% FiO₂ is not recommended. (Class III HARM, LOE B-R)
- Continued recommendation of the use of 100% FiO₂ whenever chest compressions are provided.

Neonatal Resuscitation in Resource-Limited Settings: Titrating Oxygen Delivery without an Oxygen Blender

[Marta Thio](#), et al *The Journal of Pediatrics* [Volume 165, Issue 2](#) , Pages 256-260.e1, August 2014

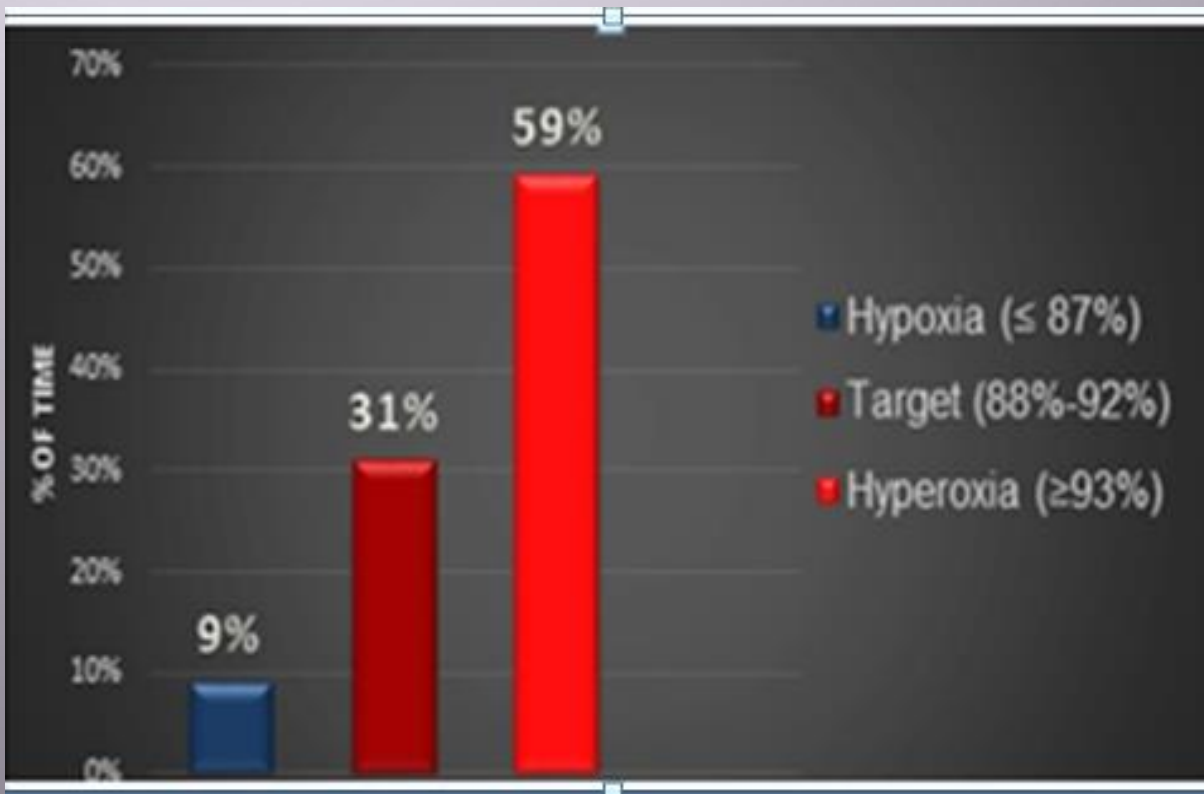
Conclusion:

- ▣ Self-inflating bags with a reservoir in situ can deliver a variety of oxygen concentrations without a blender, from <40% with 0.25 L/min oxygen flow to 100% with 5 L/min.
- ▣ The adjustment of oxygen flow may be a useful method of titrating oxygen in settings where air-oxygen blenders are unavailable.

Regulation of oxygen use in the NICU

Oxygen therapy should be targeted to levels appropriate to the condition, gestational age and postnatal age of the infant

Sink D W et al . Arch dis child . 2011



Temperature Control in the DR



- ▣ Hypothermia on admission to NICU very common: 60%
- ▣ Independently associated with increased mortality 1.6 to 1.9 times
- ▣ Plastic wrap/ plastic bag prevents evaporative heat loss in preterm infants

[Vohra et al 1999, 2004]

20 MILLION LBW babies born each year.



Do we have enough

- ▣ Incubators?
- ▣ Monitors?
- ▣ Nurses?



Kangaroo Mother Care in Low Birth weight infants

Cochrane Database Syst Rev 2014

18 studies: 2751 infants



↓ mortality: RR 0.60 [95%CI: 0.39-0.92]

↓ hypothermia: RR 0.34 [95%CI 0.17-0.67]

↓ nosocomial infection: RR 0.45 [0.27-0.76]

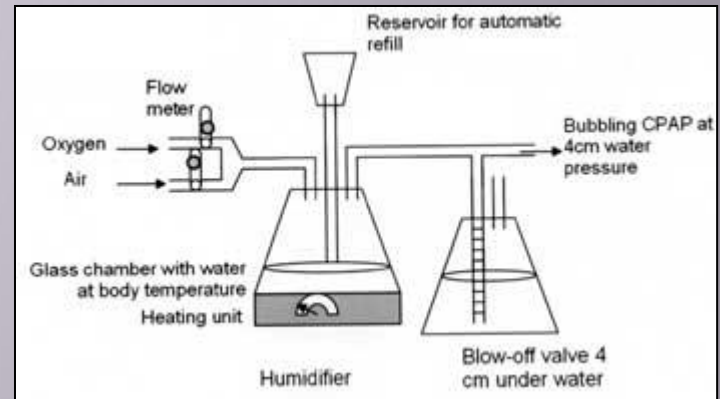
↓ length of hospital stay: mean diff 2.2 days

KMC in India



In affluence, KMC is useful addition to infant care
In financial constraints, it is a precious gift
In poverty, it may be the only means of survival

Ventilator versus CPAP



Simple calculation:

- ▣ Delivery room CPAP. Selective but early surfactant usage.
- ▣ Decreased surfactant use
- ▣ Decreased ventilator days
- ▣ Decreased VAP/ infection
- ▣ Increased survival with lower cost

Use of Human Milk in the Intensive Care Nursery Decreases the Incidence of Nosocomial Sepsis

El-Mohandes, et al. J Perinatol 1997

	Incidence of sepsis	
	Human milk	Formula
Day 0- 10	5%	10%
Day 11- 24	9%	20%
Day 25- 38	0%	15%

Odds ratio for sepsis in Human Milk fed infants = 0.4
(95% limits 0.15 to 0.95), $p= 0.04$

Human milk and neurodevelopment in preterm infants

- ▣ *Lucas A Lancet 1992, Arch Dis Child F & Neo Ed 1994*
 - 502 preemies 18 month follow up
 - **Donor milk 8.8 points > term formula**
 - 300 preemies 7.5 -8 year follow up
 - **Mother's milk 10 points > no mother's milk**
- ▣ *Vohr B Pediatrics 2006*
 - 1035 ELBW infants, 18 month follow up
 - Every 10 ml/kg/day of BM contributed to 0.53 points on Bailey Mental Development Index
 - **110 ml/kg/day breast milk = 5 points**

Feeding in the NICU

- ▣ Start feeding early
- ▣ Use mother's own milk whenever possible
- ▣ Consider increasing volume of milk instead of fortification?

A Randomized Control Trial Comparing Two Enteral Feeding Volumes in Very Low Birth Weight Babies

Thomas N, Cherian A, Santhanam S, Jana AK
J Trop Pediatr 2012

200 ml/kg/day vs 300 ml/kg/day

Simple interventions

Agarwal et al. J Perinatol 2007

- ▣ Handwashing and aseptic precautions
- ▣ Enteral nutrition
- ▣ Strict antibiotic policy
- ▣ Nursing training and involvement of nurses in decision making and administrative issues
- ▣ Involvement of mothers

Impact of simple interventions

Agarwal R, et al. J Perinatol 2007

	Control	Intervention
Neonatal mortality	29.3/ 1000	20.3/ 1000
Sepsis related deaths	37.9%	15.5%
Antibiotic use	72%	23%
Newer antibiotic use	33.8%	2.6%

Delhi Neonatal Infection Study (DeNIS) collaboration

Of the 88 636 live-births from July 2011 to February 2014,

14 779 neonates required NICU admission;

13 530 (90.0%) neonates were enrolled in the study

Incidence of total and culture-positive sepsis was 14.3% (95% CI 13.8–14.9) and 6.2% (5.8–6.6), respectively. Nearly two-thirds of total episodes occurred at or before 72 h ('early-onset').

Two-thirds of isolates were Gram-negative including Acinetobacter spp. (21.9%), Klebsiella spp. (16.6%), and Escherichia coli (13.7%).

Majority of the pathogens exhibited high degree of AMR to even 'reserve' antibiotics like extended spectrum cephalosporins and carbapenems

High proportion of Acinetobacter spp. (81.5%) and Klebsiella spp. (53.8%) was multi-drug resistant (MDR).

Colistin resistance was detected in seven (0.7%) Gram-negative isolates.

- ❑ **Avoid empirical usage of antibiotics.**
- ❑ **Develop logistics to improve and increase true culture yeilds**
- ❑ **Stop antibiotics as soon as possible.**
- ❑ **Do not higher antibiotics**
- ❑ **Do not use broad spectrum antibiotics.**
- ❑ **Antibiogram suited to the unit and local environment**
- ❑ **Have an antibioitic policy.**
- ❑ **Develop a liaison with the obstetricians and physicians in the periphery.**

Low Cost Interventions that Work for preterm infants



- ▣ Antenatal steroids
- ▣ Antenatal magnesium sulphate
- ▣ Delayed umbilical cord clamping
- ▣ Temperature control in DR
- ▣ Regulated O₂ use
- ▣ Kangaroo care
- ▣ CPAP
- ▣ Human Milk feeding
- ▣ Hand washing
- ▣ Restricted antibiotic use

THANK YOU. ✨

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