Preterm labour

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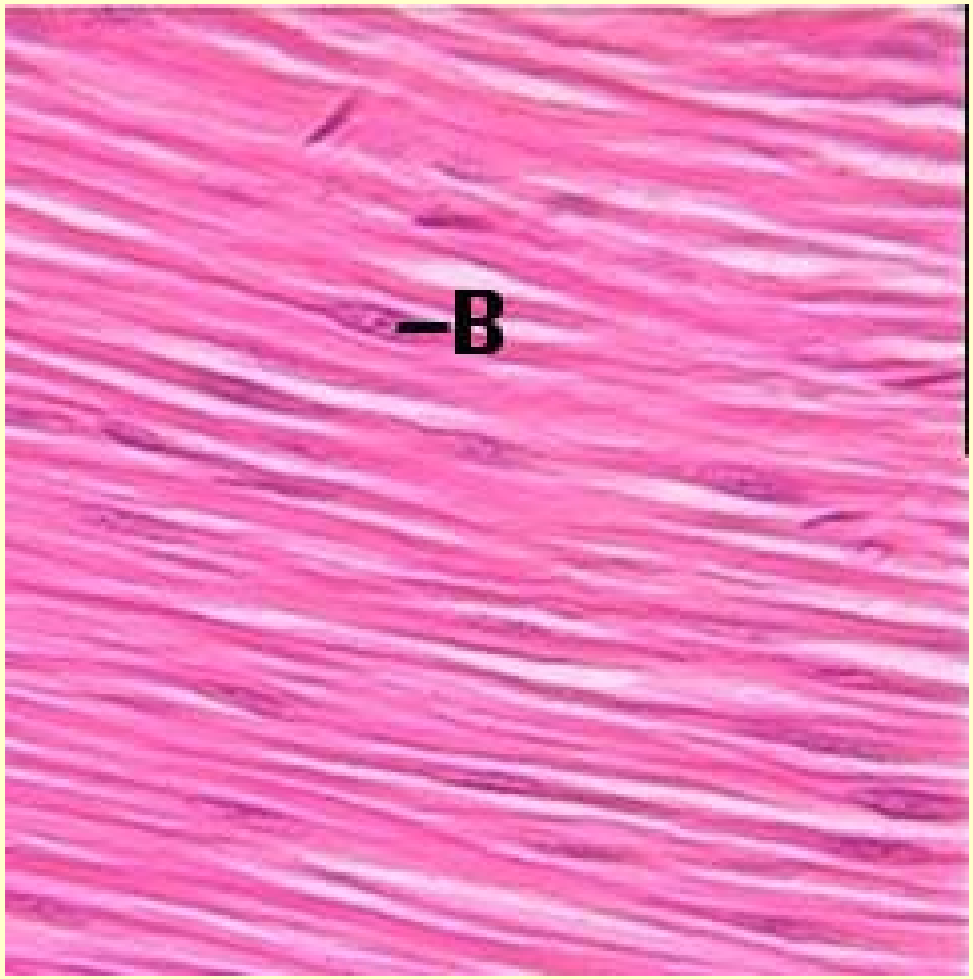
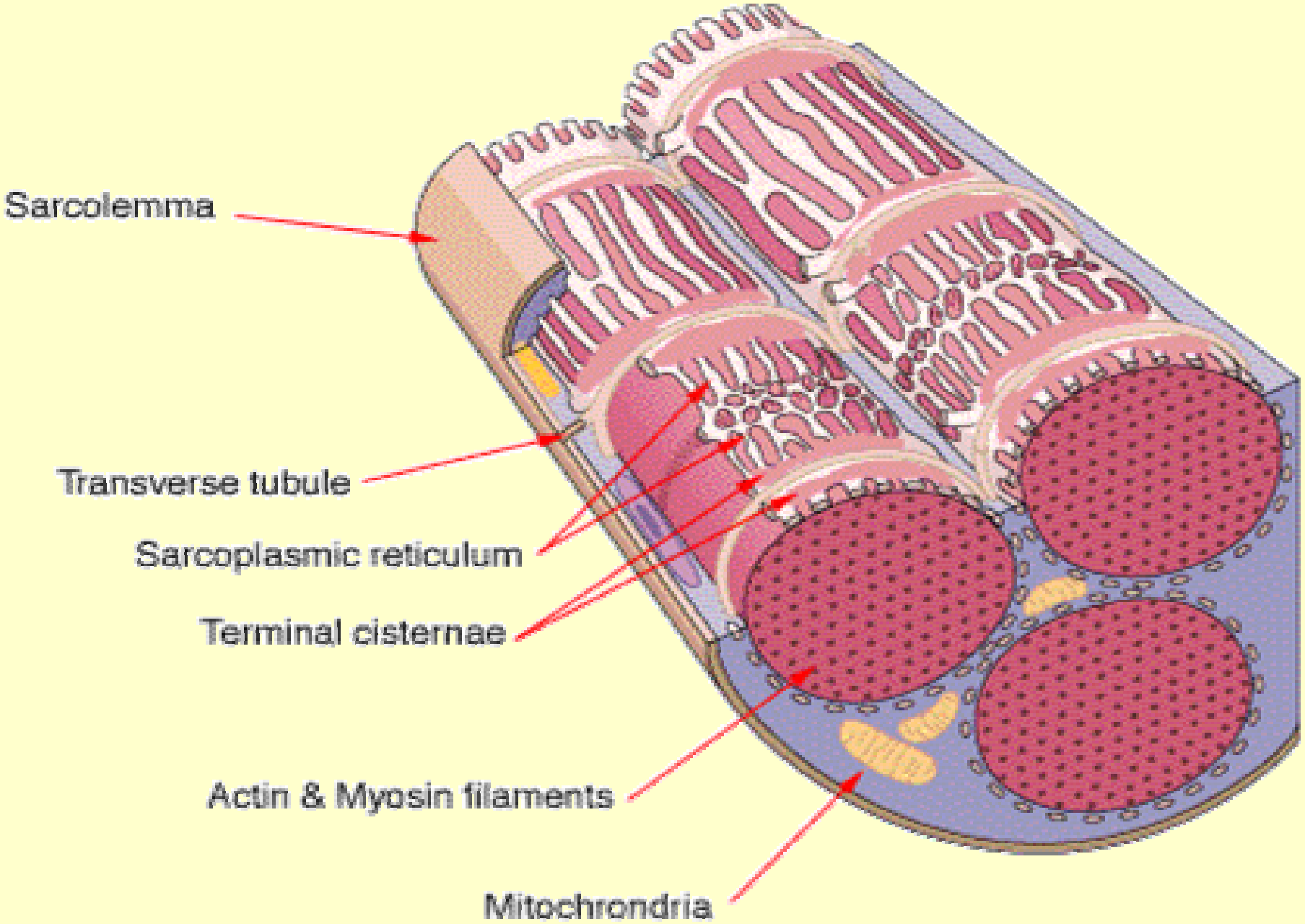
Questions

- How after 40 weeks of quiescence the gravid uterus starts to contract and produces the expulsion of the fetus?
- It is possible to understand why delivery happens too early or too late?

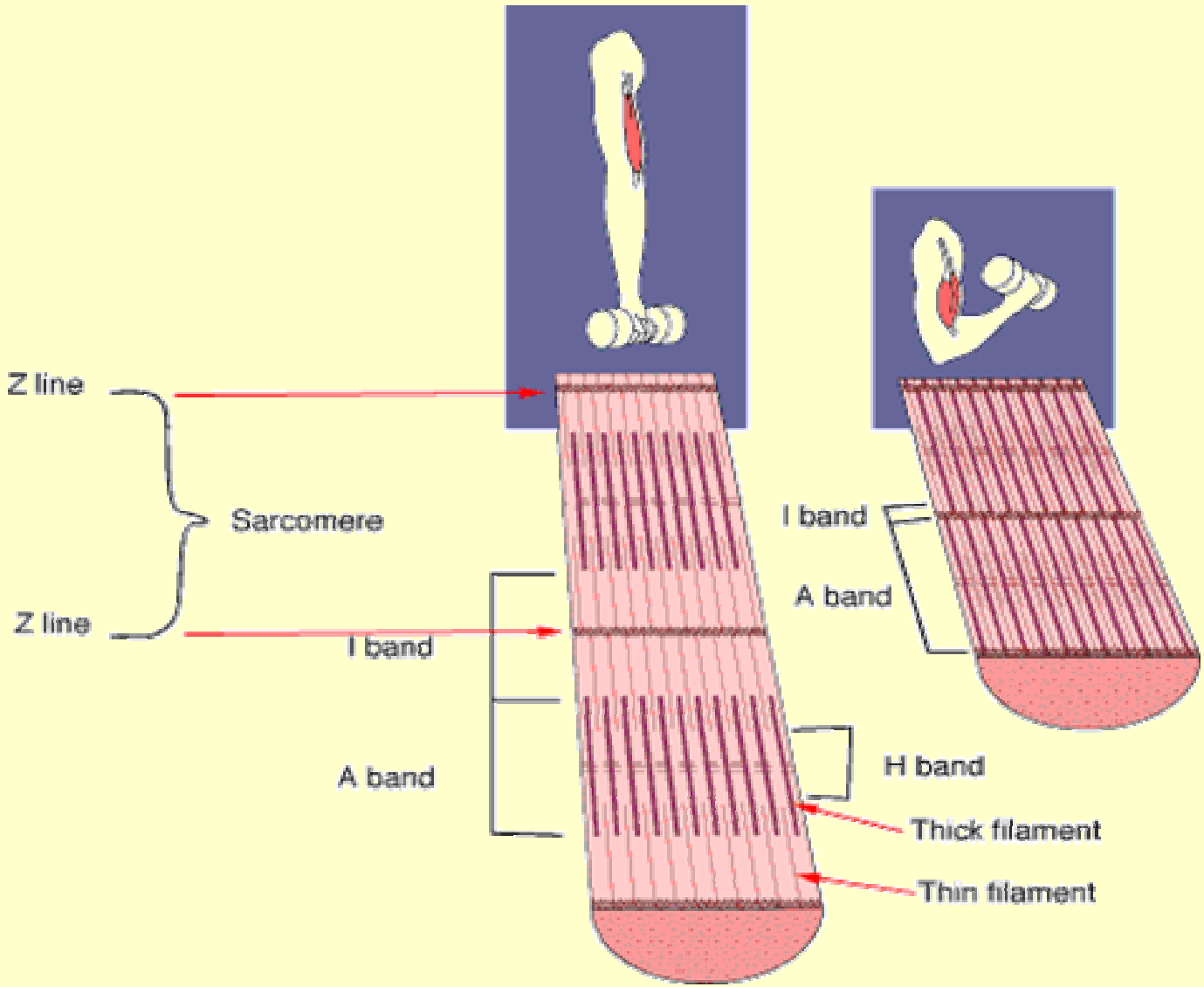
Smooth muscle



Myofibril


Sarcolemma
Transverse tubule
Sarcoplasmic reticulum
Terminal cisternae
Actin & Myosin filaments
Mitochrondria

Contraction

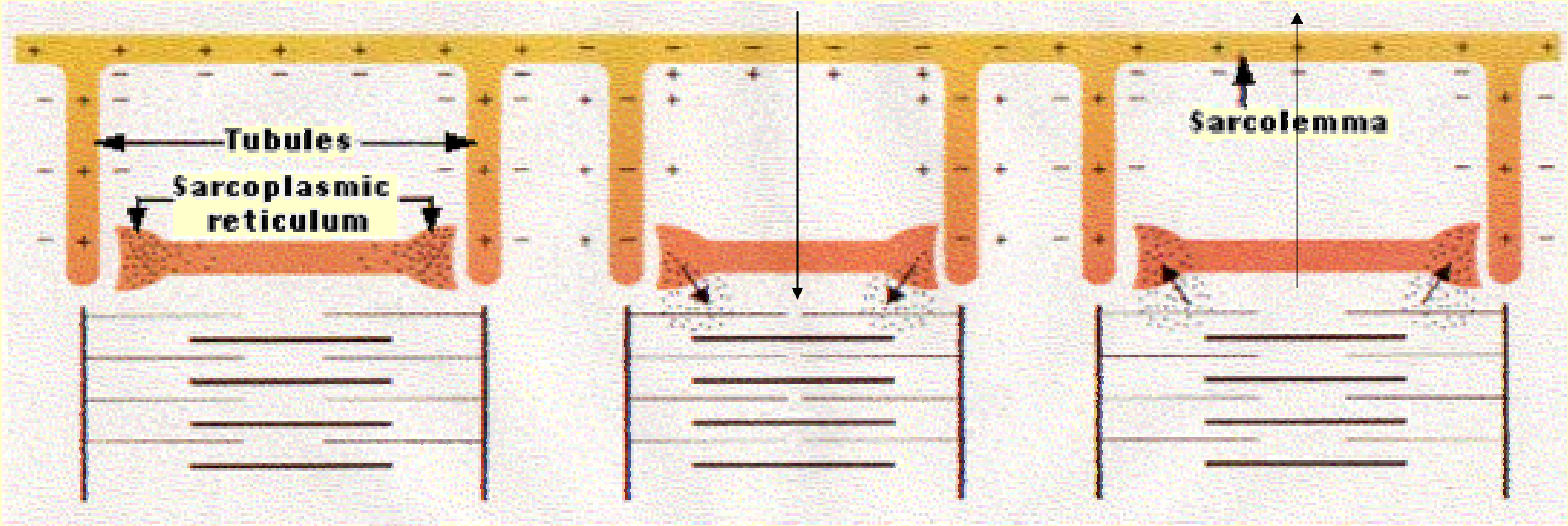


Myosin and actin

- The interaction of myosin and actin is essential to muscle contraction and depends on the concentration of intracellular calcium
- The increase in the concentration of intracellular calcium stimulates the contraction
- The decrease in intracellular calcium produces muscular relaxation

Increased intracellular concentration of calcium

- Calcium enter from the extracellular fluid
- Calcium is released by the sarcoplasmic reticulum



The T system and sarcoplasmic reticulum in resting muscle

An action potential reuerses the polarity of the tubules releasing calcium ions (dots) from the sarcoplasmic reticulum. Their binding to troponin on the thin filaments "turns on" in interaction of actin and myosin, and the sarcomere shortens.

Restoration of normal polarity is followed by return of calcium to the sarcoplasmic reticulum and relaxation of the sarcomere.

Mechanisms that regulate the intracellular calcium concentration

- Electro-chemical mechanism
- Hormonal-receptorial mechanism

Electro-chemical mechanism

- The electric activity is started by local pacemakers (muscular cells which depolarize spontaneously giving origin to action potentials)
- The action potential can propagate from one cell to the other by means of gap junctions that connect the cells
- Calcium channels sensible to voltage let the Calcium in

Hormonal-receptorial system

- Different agents may act on the myometrial smooth muscle cells to cause changes in the intracellular concentration of calcium and promote contraction or relaxation
- Examples are oxytocin, prostaglandin, beta agonists (first messengers)
- These agents acts on the permeability of the membrane to calcium by means of receptors or second messengers

The uterine phases of parturition

- Phase 0 is characterised by myometrial smooth muscle tranquillity and cervical structure integrity
- Phase 1 is the time of uterine awakening, the capacity of myometrial smooth muscle to contract is implemented
- Phase 2 is synonymous with active labour
- Phase 3 encompasses the event of the puerperium

Mechanisms of Calcium regulation and the phases of parturition

Phase 0

- Myometrial smooth muscle cell is relaxed
- The mechanisms regulating intracellular calcium concentration (electro-chemical and hormonal-receptorial) are inactive

Electro-chemical mechanism in Phase 0

- Few action potentials are discharged by the pacemaker cells
- The resting potential of the myometrial cells is too high to be altered by the action potentials discharged by the pace maker cells
- There are no gap junctions that allow the propagation of the electric stimulus

Hormonal-receptorial mechanism and Phase 0

- Insufficient production of first messengers (e.g. prostaglandins)
- Insufficient production of receptors (e.g. oxytocin receptors)
- Increase expression of proteins that favour relaxation (e.g. G-Protein)

Electro-chemical mechanism in Phase 1

- Increase in the generation of action potentials
- The resting potential of the myometrial cells reaches optimal levels that can be affected by the action potentials
- Increase in gap junctions between myometrial cells

Hormonal receptoral mechanism and Phase 1

- Increase in myometrial oxytocin receptors
- Decrease in the synthesis of G-proteins responsible for muscle relaxation

Electro-chemical and hormonal-receptorial mechanisms in Phase2

- Action potentials are discharged more frequently
- Marked increase in intracellular calcium
- Decrease degradation of first messengers (modest hypoxia due to increased tension)
- These mechanisms sustain each other and labour cannot be stopped

How the mechanism are activated?

- Specific protein control the process of inactivation and activation of the mechanisms that regulate intracellular calcium (control of ionic channels or enzymes that inactivate the first messengers)
- The synthesis of these proteins depends on the expression of genes contained in the DNA of the muscular cell

Estrogens-Progesterone Hypothesis

- Experimental studies have shown that estrogens and progesterone activate the genetic expression of proteins which influence the activities of the mechanisms that regulate intracellular calcium
- In animal models at term one can observe an increase in Estrogens and a decrease in Progesterone

Doubts on the Hypothesis

- In humans progesterone declines only after delivery
- Pregnancies with very low levels of estrogens and progesterone end with timely and normal delivery
- Progesterone at term does not prevent delivery
- Antagonists of progesterone do not trigger labour and delivery

Other hypothesis

- The rate of increase in maternal plasma corticotrophin-releasing hormone is inversely proportional to gestational length.
- As the hormone is synthesised by the placenta, it supports the suggestion that the human placenta has an important role in determining gestational length.
  (McLean and Smith, 1999; Leung et al, 2001)

Two mechanisms for premature delivery

- Progression to Phase 1 for the activation of both the electrochemical and the hormonal receptorial mechanism and increase of the intracellular calcium (similar to term delivery)
- Activation of only the hormonal receptorial system due to abnormal production of first messengers which stimulate contraction (e.g. induction with prostaglandins, infections) - could be stopped -.

Public Health considerations

- Increase awareness that preterm infants require special care
- In the US prematurity was identified as the most frequent cause of death in 1949 when birth certificate included gestational age and birthweight
- Countries with higher rate of preterm delivery have higher rates of infant mortality

Definitions (WHO 1961)

- Prematurity: delivery before 37 weeks
- Low birth weight: birth weight 2500 grams
- Small for gestational age: birthweight below the 10th percentile for gestational age

Impact of preterm birth

- Low birth weight and prematurity are associated with neonatal mortality
- Is there a lower limit for survival?
- Critical points:
  - 1000 grams
  - 22-25 weeks (consider morbidity: of the infants who survived at 23-24 weeks virtually all had significant brain abnormalities Allen et al, 1993)

Upper limit for significant prematurity

- Is there a birthweight or gestational age threshold after which attempts to delay delivery are unwarranted?
- Between 32 and 34 weeks the incidence of complications attributable to preterm delivery becomes indistinguishable from term infants (Robertson et al, 1992)
- Similar results were observed for infants of approximately 1900 grams (DePalma et al, 1992).