Effects of ionising radiation on the developing embryo: the classical view

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Introduction

- Many pregnant women are concerned about the possible consequences of exposing the unborn child to toxic chemicals or to radiation
- Bigger concern among pregnant patients and radiation workers exposed to ionizing radiation each year
- For many patients, exposure is appropriate, while for others exposure may be inappropriate
- Lack of knowledge responsible for great anxiety and probably unnecessary termination of many pregnancies

Aim: overview of the current knowledge on the potential effects of an exposure of the developing embryo to ionizing radiation

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Effects of *in utero* irradiation: general background

- Prenatal doses from most properly done diagnostic procedures present no measurable increased risk of prenatal death, malformation, or impairment of mental development over the background incidence of these entities
- Higher doses, such as those involved in therapeutic procedures, can result in significant foetal harm
- Radiation risks throughout pregnancy are mainly related to the stage of pregnancy and the foetal absorbed dose

Effects of *in utero* irradiation: general background

- Clinical radiation effects are due either to
  - **Cell killing** (lethality, CNS anomalies, cataract, growth retardation, malformations, behavioural disorders):
    - - practical threshold

    - the higher the dose above the threshold, the more severe the effect

    → “deterministic effects”

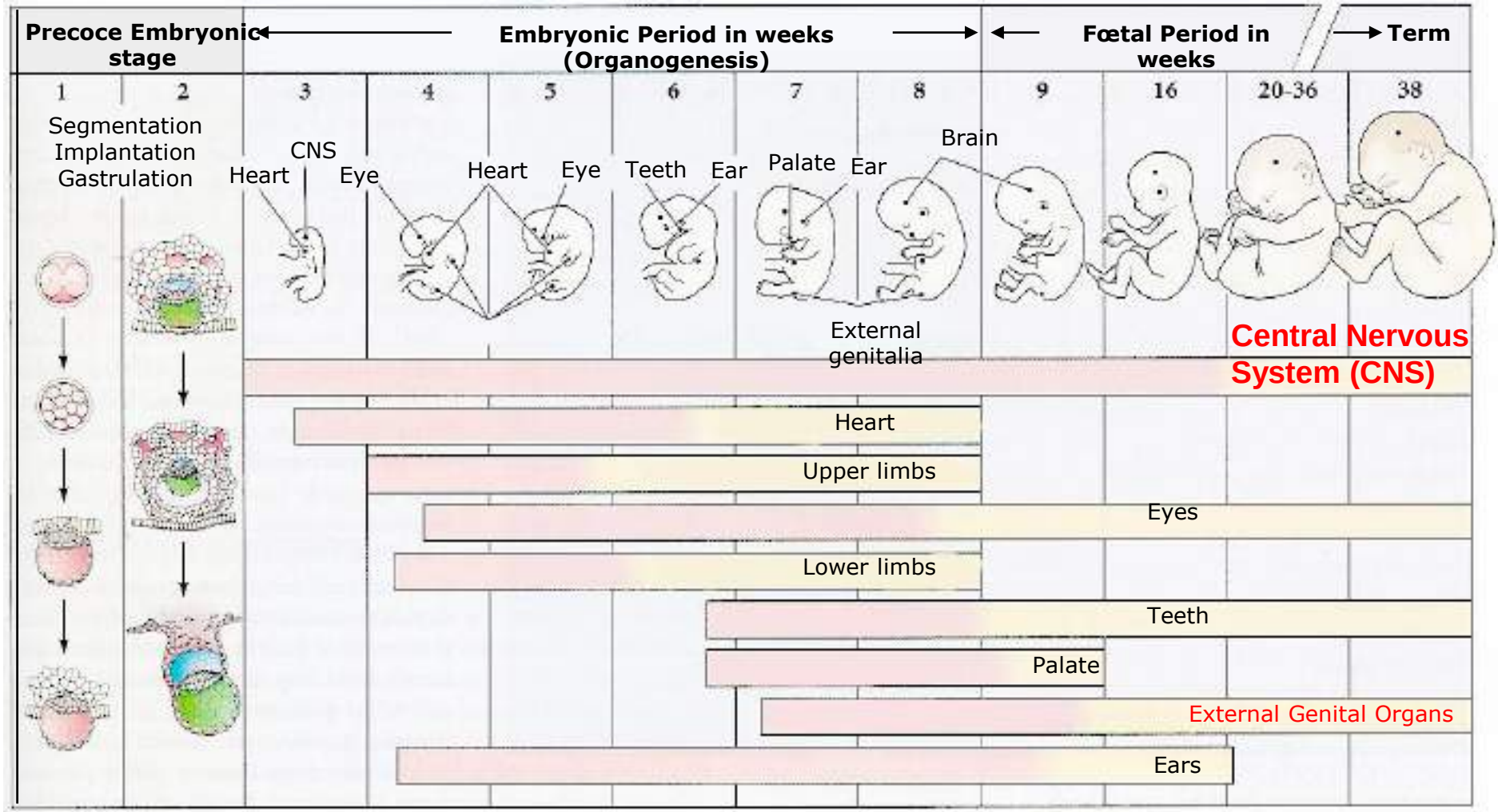
  - **Unrepaired/misrepaired DNA damage** (leukaemia, cancer and potential hereditary effects):

    the probability of such effects increases with the dose, with no identifiable threshold dose below which the chance is known to be zero

    → “stochastic effects”

- Protracted exposures are expected to have less overall effects than acute exposure

Embryonic risks depend on the developmental stage at the time of irradiation



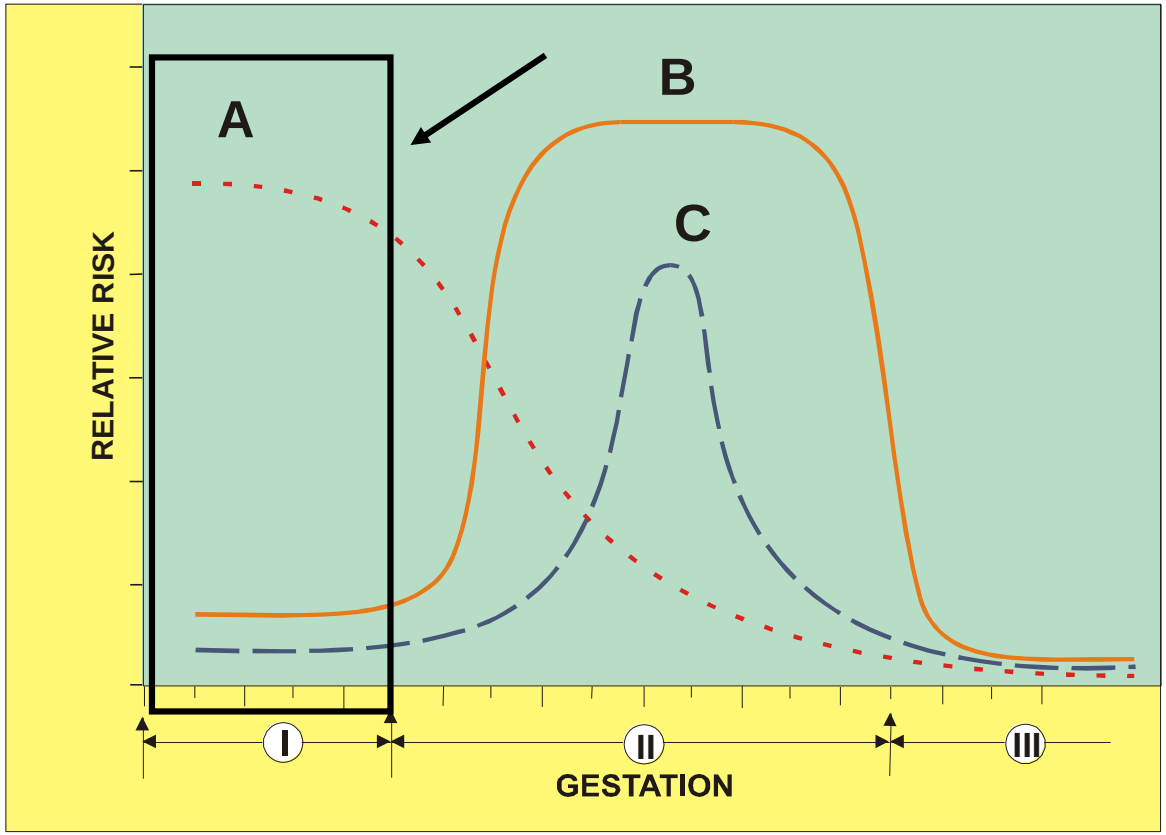
Lethal Malformations

• **Frequent Site of action of teratogens**

Major Congenital Malformations

Functional defects and minor morphological malformations

Sensitivity of the embryo to radiation-induction of developmental effects (results of animal experiments)



A) **Prenatal death**
B) Anomalies
C) Neonatal death

I **Pre-implantation period**
II Organogenesis
III Histogenesis (Foetal period)

Sensitivity to radiation induction of mortality: the pre-implantation period

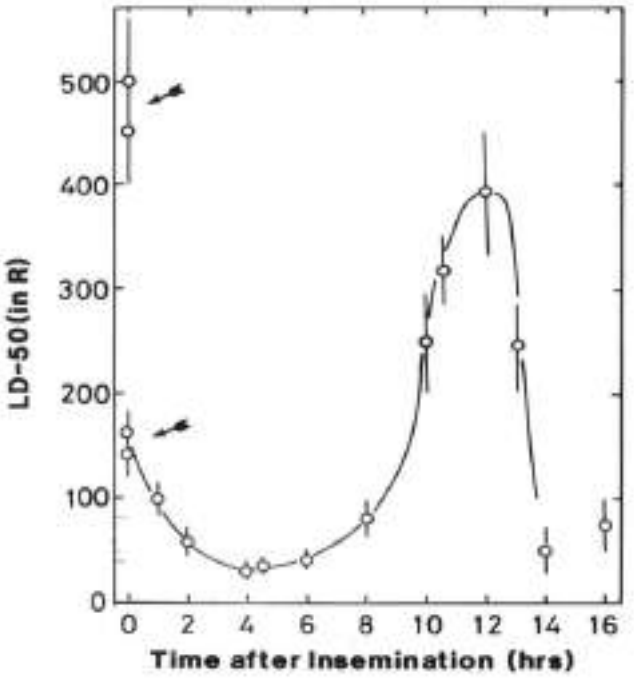
- Sensitivity highest at the unicellular stage or “1-cell stage”

  - DL50 : 0.4 Gy 4-6 h post fertilization….but

  - DL50 : 4 Gy 12 h post fertilization

  → sensitivity related to the cell cycle phase

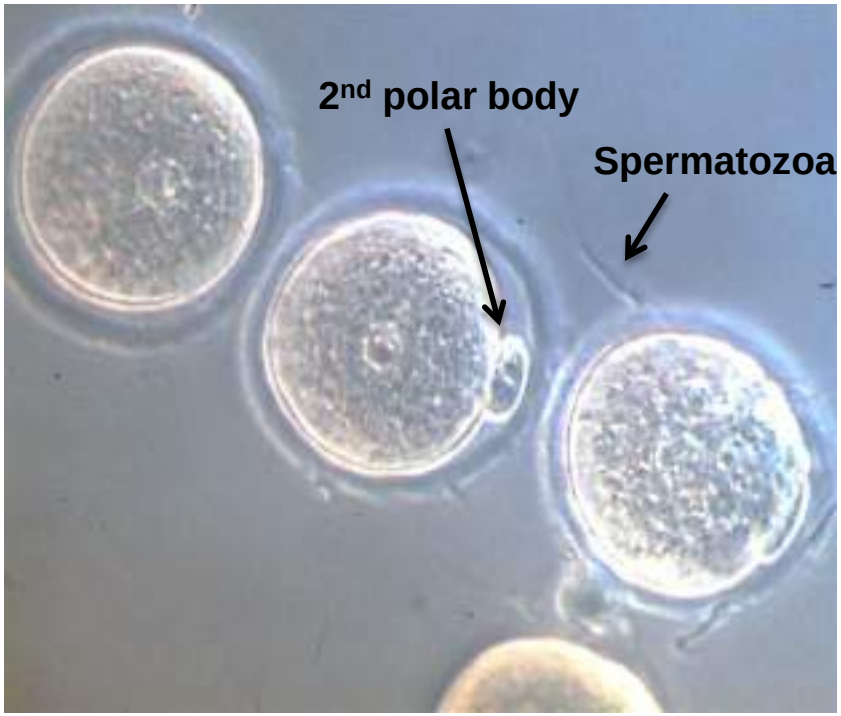
- Sensitivity decreases during following stages, since cellular death can be compensated by other (undifferentiated) cells
- Risk: failure to implant or undetectable death of the conceptus
- ICRP 2005 : “At doses of a few tens of mGy, such effects will be very infrequent”



(Yamada et al, 1982)

The pre-implantation period

Fertilization (picture by T. Yamada)



1-cell embryos

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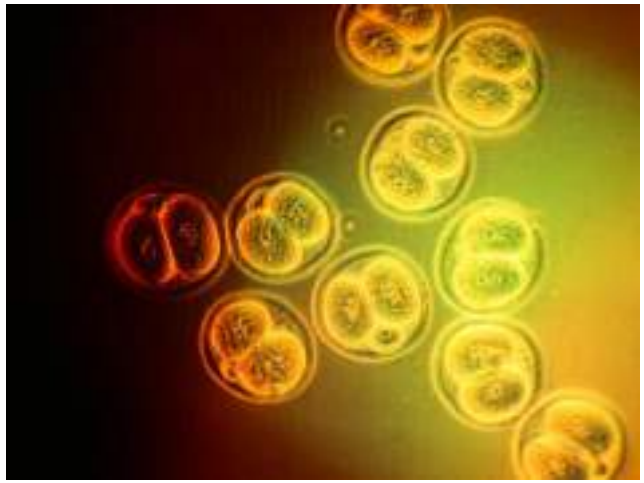
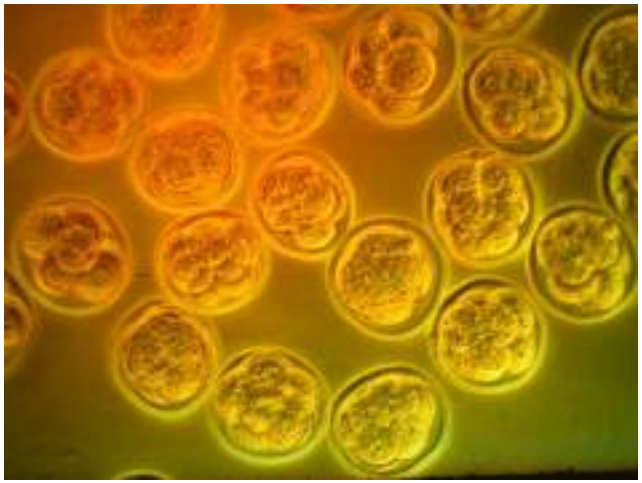
The pre-implantation period

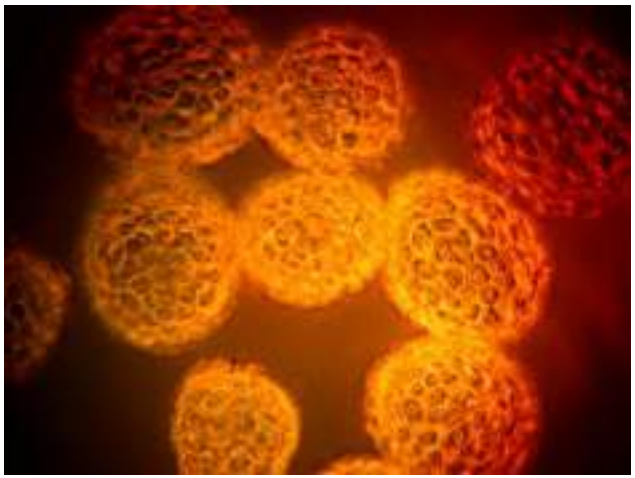


2-cell stage



6-8-cell and morula stages

Morulas



Blastocysts ready to implant

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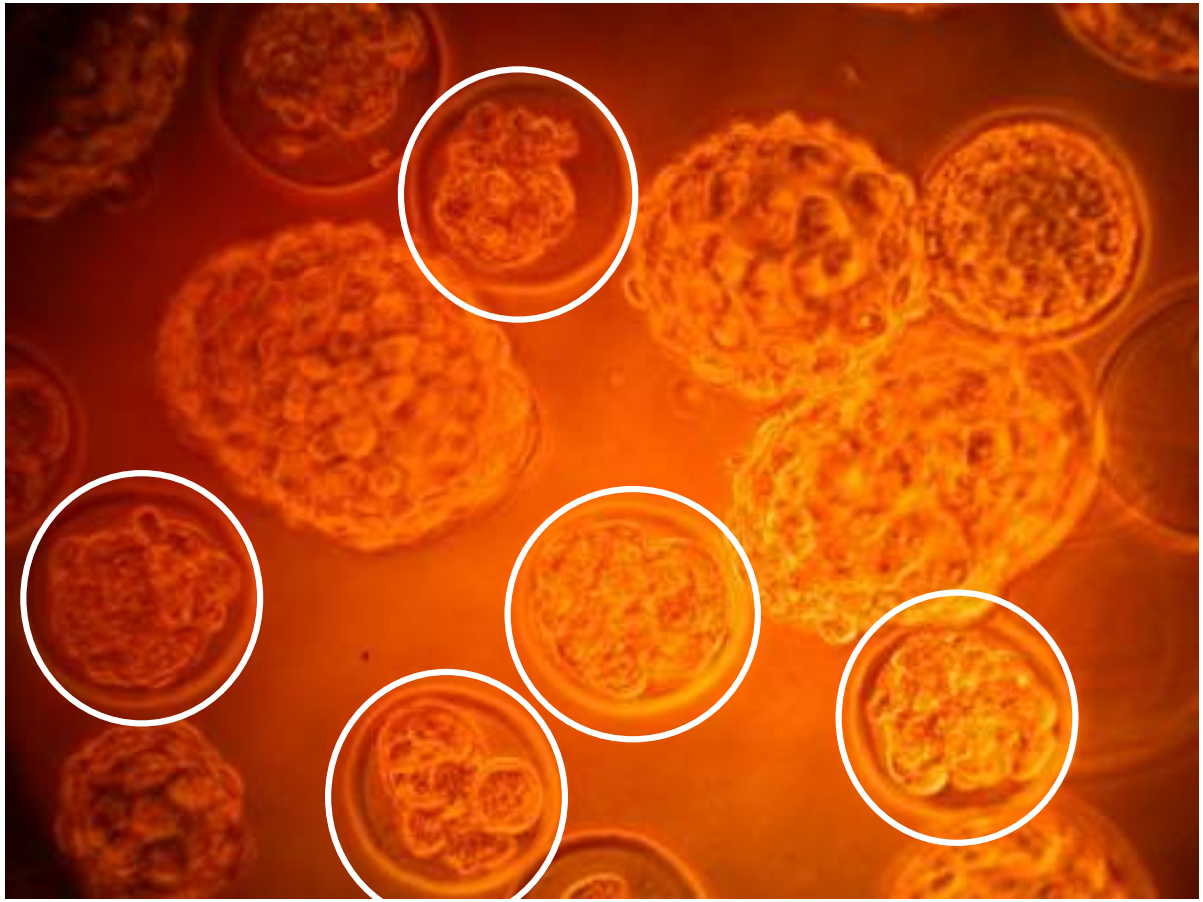
The pre-implantation period



Pre-implantation development after X-irradiation (1Gy) at the 1-cell stage: dead embryos (white circles)

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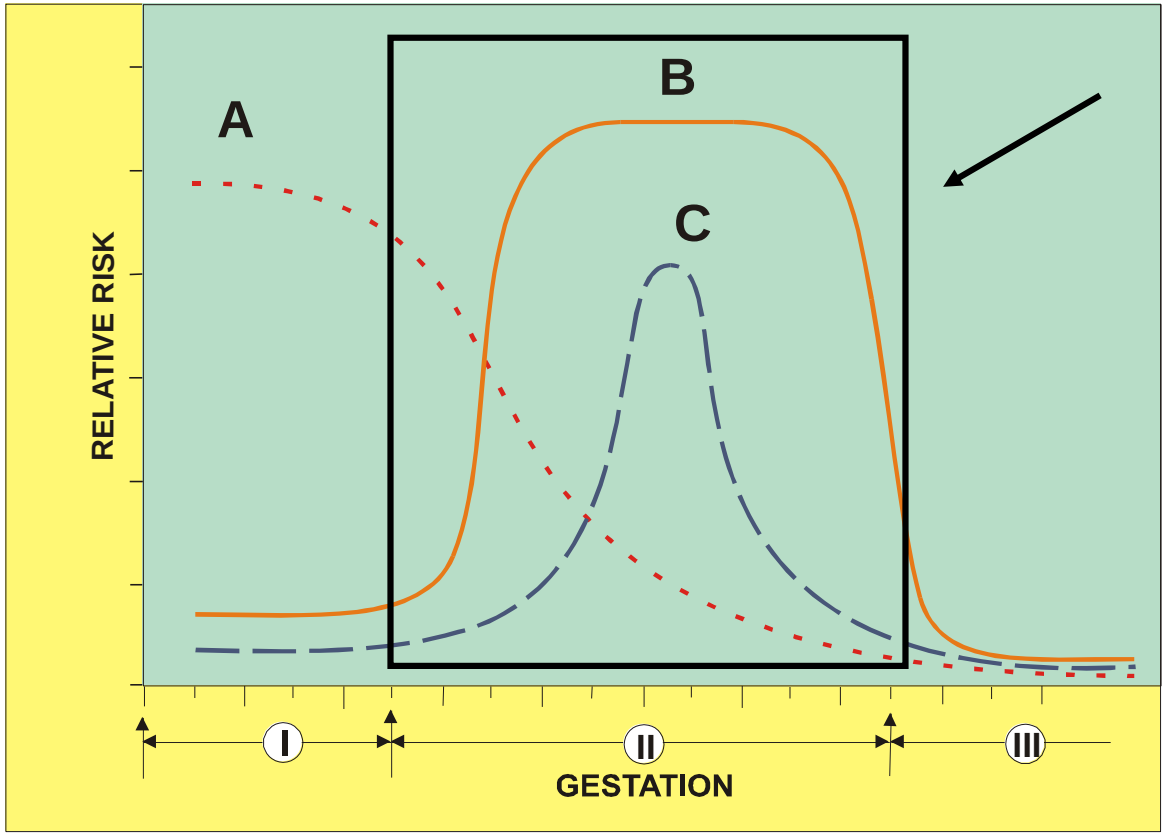
Chromosome aberrations (fragments) in an irradiated mouse 1-cell embryo

These fragments will lead to early embryonic mortality

Sensitivity of the embryo to radiation-induction of developmental effects (results of animal experiments)



A) Prenatal death
B) **Anomalies**
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I Pre-implantation period
II **Organogenesis**
III Histogenesis (Foetal period)

Sensitivity to radiation induction of congenital abnormalities: the organogenesis period

- **Congenital anomaly: gross or microscopic structural defect present at birth, whether detected at that time or not**

- Malformation is produced at a specific time point during development. This time point coincides with main stage of differentiation and organization of the considered structure (period of sensitivity to induction of each malformation is specific to each species)

- Increasing the dose results in an extension of the period of sensitivity and an increase of the incidence of malformations
- Dose-effect relationship generally sigmoid, the frequency of malformations per unit of dose increasing with the dose
- **Threshold : 100 mGy**

Sensitivity to radiation induction of congenital abnormalities: the organogenesis period

- **Growth retardation :**

- Expressed as a weight reduction at birth : results from cell depletion
- Recovery quite possible, smaller new-born may reach normal weight as adults

Dwarf foetus
with **exencephaly**

Normal foetus

Dwarf : the body appears normally proportioned, but is clearly abnormally small (weight is less than 75% of the mean weight of the other foetuses from the same group)

Foetal doses following common diagnostic procedures (NRPB, 1998)

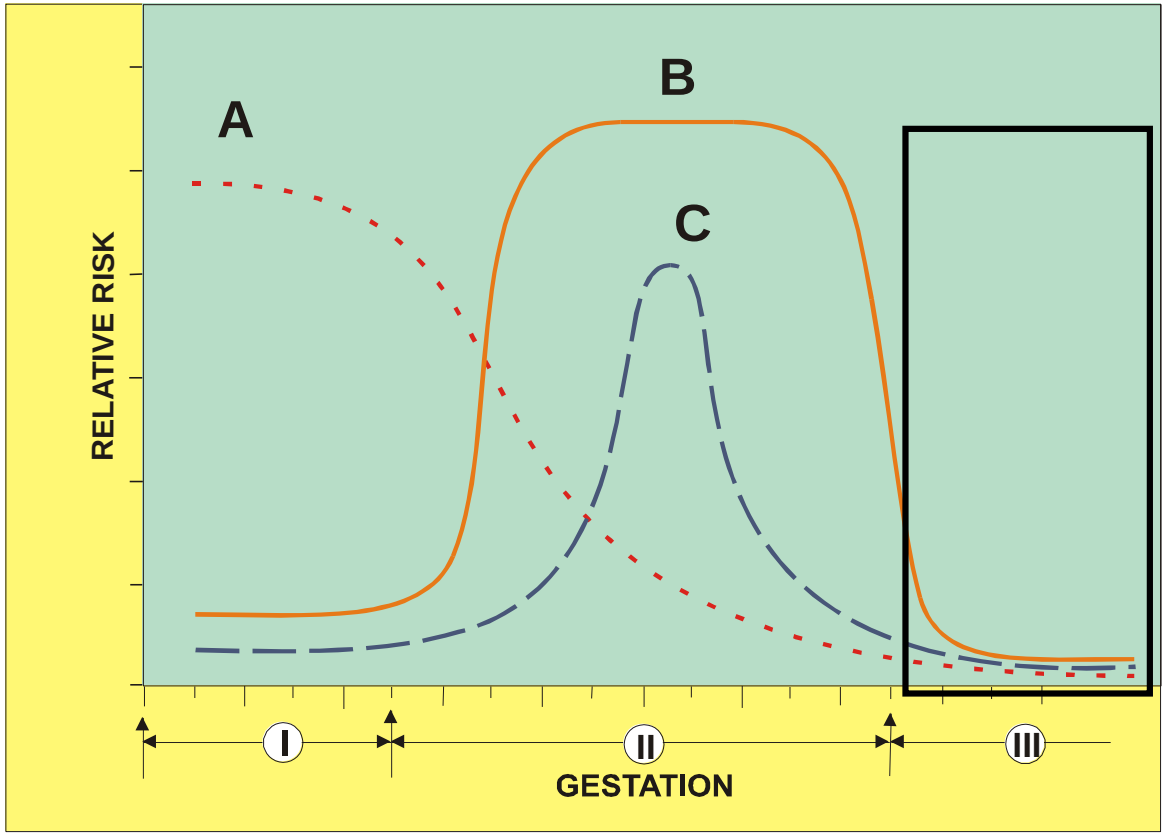
TABLE 2 Fetal doses following common diagnostic procedures; taken from UK surveys of diagnostic radiology and nuclear medicine[4,8]

EXAMINATION/PROCEDURE	FETAL DOSE (mGy) MEAN	MAXIMUM
Conventional x-ray		
Abdomen	1.4	4.2
Barium enema	6.8	24
Barium meal	1.1	5.8
Chest	<0.01	<0.01
Intravenous urography	1.7	10
Lumbar spine	1.7	10
Pelvis	1.1	4
Skull	<0.01	<0.01
Thoracic spine	<0.01	<0.01
Computed tomography		
Abdomen	8.0	49
Chest	0.06	0.96
Head	<0.005	<0.005
Lumbar spine	2.4	8.8
Pelvis	25	79
Pelvimetry	0.2	0.4
Nuclear medicine		
^{99m}Tc bone scan (phosphate)	3.3	4.6
^{99m}Tc lung perfusion (MAA)	0.2	0.4
^{99m}Tc lung ventilation (aerosol)	0.3	1.2
^{99m}Tc kidney scan (DTPA)	1.5	4.0
^{99m}Tc thyroid scan (pertechnetate)	0.7	1.6
^{99m}Tc dynamic cardiac scan (RBC)	3.4	3.7
^{51}Cr glomerular filtration (EDTA)	<0.01	0.01
^{201}Tl myocardial perfusion (thallium)	3.7	4.0
^{99m}Tc brain scan (pertechnetate)	4.3	6.5
^{75}Seleno-cholesterol	–	14.0
^{67}Ga tumours and abscesses	–	12.0
^{131}I thyroid metastases	–	22.0

Note Fetal doses cited are those assumed from estimates of uterine dose.

- Threshold dose for malformations higher than what is reached in most diagnostic radiology or diagnostic nuclear medicine
- 100 mGy not likely reached with 3 pelvic CT scans, nor with 20 conventional diagnostic X-rays of the abdomen or pelvis

Sensitivity of the embryo to radiation-induction of developmental effects (results of animal experiments)



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I Pre-implantation period
II Organogenesis
III **Histogenesis (foetal period)**

The foetal period: a period of lower radiation sensitivity

- Exposure of rodent embryos during the foetal period: much less spectacular effects
  - → **anomalies in development of tissues**
  - → **general or localized growth retardation**
- **Growth retardation frequently persists** during all extra-uterine life (>< irradiation during organogenesis)
- Other effects at fairly high doses: hematopoietic system, liver and kidney
- Gonads: a few hundreds mGy needed to produce fertility changes

The child on the right was exposed to radiation during the second trimester resulting in growth retardation (Brent 1986).

Embryonic radiation sensitivity during pregnancy: experience in humans

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Malformations and effects on the central nervous system

- **Radiation-induced malformations are exceptional in humans**
- **Hiroshima and Nagasaki : *in utero* exposure during weeks 8-15 or, at a lesser extent, during weeks 15-25, can lead to a mental retardation associated or not to microcephaly**
- Foetal doses > 100 mGy may result in a decrease of the IQ (at a foetal dose of 1 Gy during weeks 8-15: reduction of IQ by about 30 points)
- Foetal doses in the range of 1,000 mGy result in a high probability of *severe* mental retardation (at a foetal dose of 1 Gy during weeks 8-15: probability of severe mental retardation = 40%)

- "Normal" incidence of
  - Mental retardation (IQ below 70): 3 %
  - SMR (in which affected individuals are unable to care for themselves): 0.5 %

A-bomb survivors irradiated *in-utero*, with microcephaly

Embryonic radiation sensitivity during pregnancy: experience in humans

Childhood Cancer

- Oxford survey of childhood cancer *(Stewart et al, 1987)* : association between diagnostic levels of *in utero* irradiation and childhood cancers (solid tumors and eukemia before 15 years)
- Other clinical studies either confirmed *(MacMahon (USA): leukemia)* or rejected the excessive risk of childhood cancer.
- Uncertainties:
  - Causal relationship ? Radiation concerned population that needed closer medical attention *(obstetrical examinations)*
  - Experimental animal studies have not supported the Oxford study results
  - Data from Japanese survivors of the bombing didn't show an increase in childhood cancer after *in utero* exposure

- Scientific community accept the association between increased risk of childhood cancer and *in utero* irradiation with a constancy of risk during all pregnancy

Summary :
Effects of a prenatal irradiation

- **Pre-implantation period:**
  - Malformations unlikely or very rare
  - Main effect is failure to implant or undetectable death of the conceptus: (all or none rule)
    - "spontaneous" abortion rate: 15 % or greater

- **Organogenesis period:**
  - Embryo is sensitive to congenital malformations
  - Malformations with a threshold of 100 mGy or higher (more than what is reached in most diagnostic radiology or diagnostic nuclear medicine procedures)
  - "spontaneous" major congenital malformations rate: 2-4 %
  - "spontaneous" intrauterine growth retardation rate (mostly due to hypertension): 4 %

- **Foetal period:**
  - The foetus is more sensitive to functional defects (mental retardation)
  - Decrease of IQ or severe mental retardation possible if exposure during weeks 8-25, and especially weeks 8-15
  - spontaneous frequency of mental retardation : 3% mental retardation, 0.5 % severe mental retardation.

- **Leukaemia and childhood cancers:**
  - It is accepted that there is an association between *in utero* irradiation and childhood cancer
  - The risk of childhood cancer remains the same throughout the pregnancy
  - 40 % increase of the background risk (0.2-0.3%) after 10 mGy → 0.3-0.4% (this is probably overestimated)
  - Throughout pregnancy, embryo/foetus at the same risk as children (2-3 times higher than whole population with its normal age distribution)

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