The Fear of Drugs in Pregnancy: Justified or Exaggerated?

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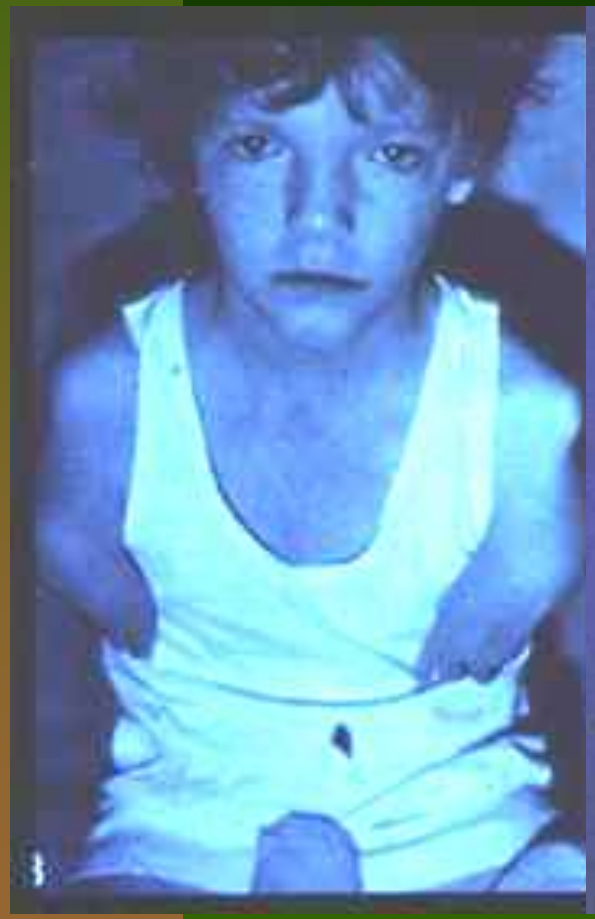
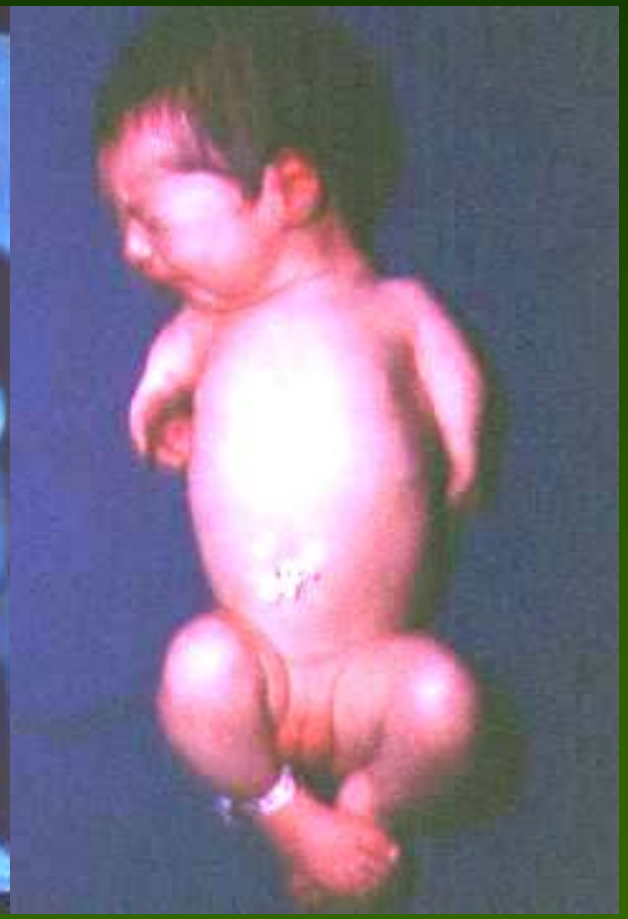
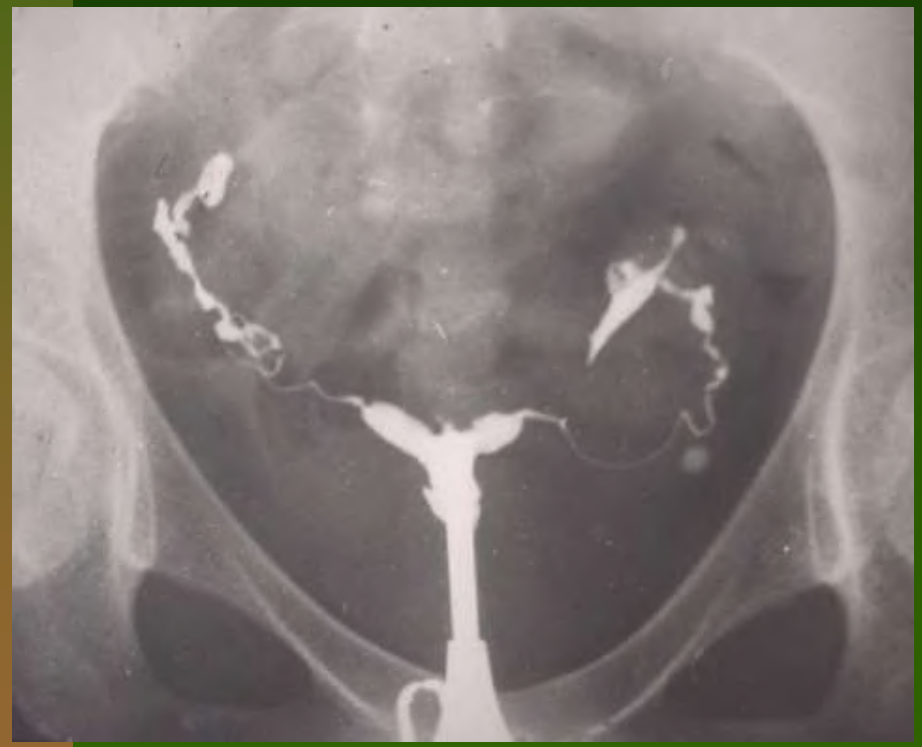
Thalidomide





- Amelia, phocomelia
- Ear anomalies
- Aplasia of gall bladder, kidneys
- Absent middle lobe of lung
- Intestinal atresia

DES



- T – shaped uterus, constriction bands
- Cervical hood
- CA cervix
- CA Vagina
- High incidence of infertility & miscarriage

Voluntary Reporting

- Only detects anomalies after event.
- Not all adverse effects are reported
- Reporting may be biased due to an incident with a related drug
- However, thalidomide & DES found by voluntary reporting

Principles of Drug Use

- Does drug cross placenta?
- Often based on MW. If < 1,000 daltons – crosses
- Is there human data?
- In most cases - none, or limited data.
- It was thought that drug could cause harm if animal dose ≤ 10 times the human dose.
- However, using data from animal data for 311 drugs raised the possibility of human embryo-fetal harm in only 75 (24%) of the drugs (Koren et al, 2003)
- Harmful effect is dose dependent

Principles of Teratogenesis

- Stage of Development
  - Organogenesis from days 13 – 60. (2-11 weeks)
    - 4 weeks – limb bud, closure of neural tube, cardiac tube & loop
    - 5-6 weeks – foot/hand plates, digital rays, cerebral hemispheres, cardiac septation, gonads differentiate, palate forms
    - 7 weeks – rotation of limbs, sex ducts, external genitalia
    - 11 weeks – cerebral cortex, metanephric kidney, palate finally closes
    - Until Birth – ASD
    - Rubella - 4 weeks eye, 6 weeks all, 8 weeks ear & Heart
  - After Oranogenesis, no teratogenic effect
- Genotype
  - Cortisone produces cleft palate in Strain A mice but not C57.
  - Animal data may not be applicable to humans

Regulation: Regulatory Agencies

- U.K. - Medical & Health Products Regulatory Agency, (MHRA) after advice from Committee of Safety of Medicines
- U.S. - FDA
- EU - European Medicines Agency
- Japan - Pharmaceutical and Medical Devices Agency (PMDA).
- Australia - Australian Drug Evaluation Committee (ADEC)
- Pharma companies need to spend vast amounts of money to convince each agency separately.
- Prices of new drugs increase

FDA Classification

	Reccommendations
Category A	Well controlled studies – No risk to fetus in the 1st trimester (and no evidence of risk in later trimesters).
Category B	Animal studies have shown risk to the fetus, but no adequate studies in pregnant women.
Category C	Animal studies have shown adverse effect on fetus, but no adequate studies in humans. Potential benefits may warrant use despite potential risks.
Category D	Human fetal risk based on investigational or marketing experience or studies in humans. But potential benefits may warrant use despite potential risks.

Category X

- The risks of drug in pregnant women clearly outweigh potential benefits.
- i:e studies in animals or humans have demonstrated fetal abnormalities
- Or drug is thought to have no use in pregnancy. If there is no use, risk obviously outweighs benefit e:g. hCG
- Category X ≠ Teratogen
- Hence Category X is confusing and misinterpreted

Problems with FDA Classification

- Drugs, once on the list were rarely reclassified
- For thalidomide, Distillers, Diaego, Grunenthal have paid £37.5 million in U.K. $A89 in Australia
- Many drugs companies do not want to touch pregnancy.
- Pharma companies will not sponsor research in pregnancy.

FDA: Pregnancy and Lactation Labeling Final Rule (PLLR)

- **Pregnancy** (includes Labor and Delivery):
  - Pregnancy Exposure Registry
  - Risk Summary
  - Clinical Considerations
  - Data
- **Lactation** (includes Nursing Mothers)
  - Risk Summary
  - Clinical Considerations
  - Data
- **Females and Males of Reproductive Potential**
  - Pregnancy Testing
  - Contraception
  - Infertility

Problems of Classification Systems

- If the physician goes against the guidelines, damages can be very heavy.
- Final Rule classification does not give instructions. Physician is liable

Doxyllamine/B6

- Doxyllamine/B6 a P
- Administered to 2 n U.S. from 1956 to 1983,
- 1960s - 1970s, lett cal journals reported association betwee fects. The media reported stories, & icity campaigns claiming that Benc
- Suspected defects: ities, cardiac defects, oral clefts, and ger etc.

San Francisco Examiner
October 19, 1980

The New Drug

BENDECTIN AND BIRTH DEFECTS

Doxyllamine/B6

- 1983 - 300 pending lawsuits.
- Bendectin voluntarily withdrawn from the U.S. market based on financial concerns.
- Insurance premiums $10 million / year. Total income from Bendectin - $13million.
- For next 30 years, no medications approved by FDA for NVP.
- Doxyllamine/B6 combination still used in Canada
- 16/6/94, $19.2 M award for boy born with club feet after his mother had taken Bendectin (CNN)

Doxyllamine/B6

- 1980 - FDA reviewed 13 epidemiologic studies, 11 found no association of Bendectin with increased birth defects
- 25% of U.S. pregnant women used Bendectin in 1978 - 1980
- Incidence of birth defects in 1985-1987 (after withdrawal) similar to 1978-80
- Figures incompatible with drug teratogenicity.
- Hospital admissions in US for NVP ↑ from 7/1000 live births to 16/1000 live births between 1981 - 1987.
- Recently, FDA approved Doxyllamine/B6 for use in pregnancy
- Are electrolyte imbalances from starvation & dehydration better than effective antiemetics?
- Where is the balance?

Metronidazole

WARNING

Metronidazole has been shown to be carcinogenic in mice and rats. (See PRECAUTIONS.) Unnecessary use of the drug should be avoided. Its use should be reserved for the conditions described in the *Indications and Usage* section below.

- Metronidazole crosses placenta & enters fetal circulation.
- Reports of increased risk of cleft lip in rodents
- Mutagenic in bacteria.
- Prolonged high-dose exposure of mice - increased incidence of lung tumors & increase in lymphoreticular neoplasia
- FDA Group B

Metronidazole

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- Metaanalyses (Caro-Paton et al, 1997) & cohort studies (Koss et al, 2012) have shown no increased risk in humans
- However, T. vaginalis infection is associated with preterm delivery and PROM
- Which is preferable – Trichomonas infection or Rx with metronidazole?
- How many abortions have been performed for metronidazole exposure?

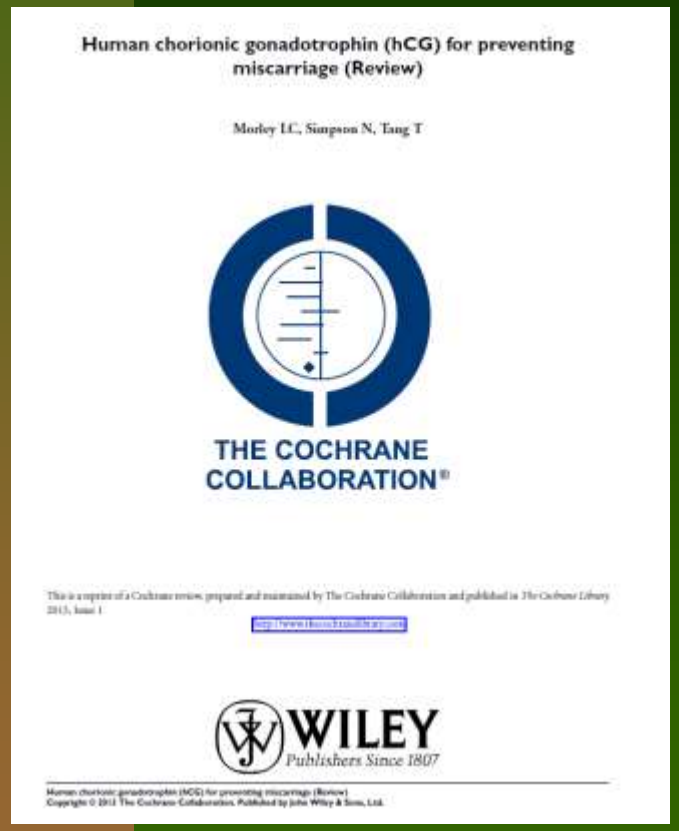
Progestogens

- Category X until used for luteal support in IVF
- 81 cases of masculinization of female external genitalia with norethisterone (from 1950s and early 1960s to prevent miscarriage) (Loose et al, 2006)
- 1989 - after determining that progestogens did *not* cause birth defects, FDA required warning: past reports of increased risk of hypospadias in male fetuses (antiandrogenic) & and mild virilization of external genitalia in female fetuses (proandrogenic)
- OR of 3.7 (95% CI, 2.3-6.0) for hypospadias (Carmichael et al, 2005)
- No reported cases with dydrogesterone

hCG

- Combined HCG/PMS (pregnant mare's serum) induces external congenital anomalies in mice offspring in a dose-dependent manner.
- Intrauterine death and impaired parturition in pregnant rats administered three times the maximum human dose based on body surface area.
- Potential extrapolation to humans has not been determined
- Why is it FDA category X not B

hCG



- Metaanalysis of hCG to prevent subsequent miscarriages in recurrent miscarriage
- No side-effects or adverse effects of hCG in any of the included studies.
- As such hCG is safe to be used. More RCTs required
- FDA should reclassify from X to B

Anti-hypertensives
(Khedun et al, 2000)

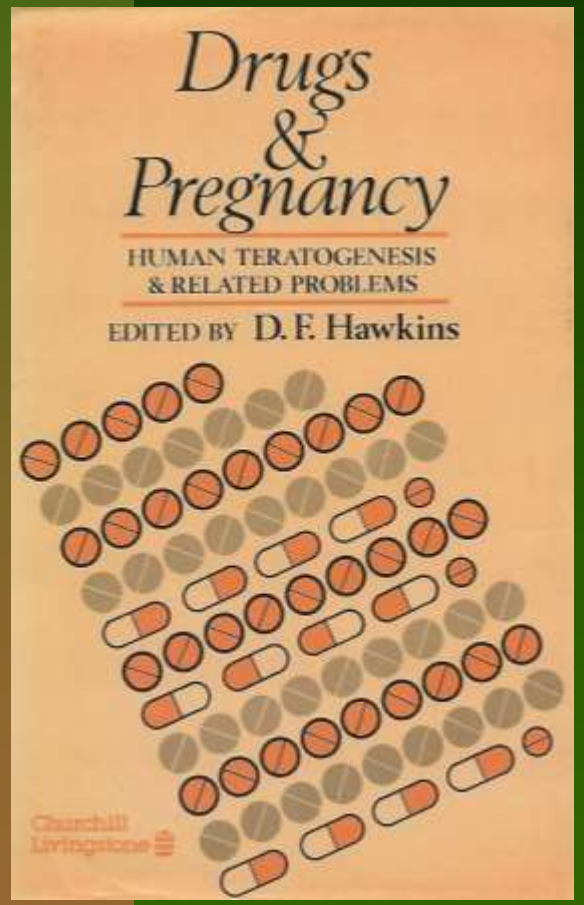
Drug	Early Pregnancy	Late Pregnancy
Methyl Dopa	Safe	Safe
Nifedipine	Maternal Hypotension	Hypotension, fetal distress *
Labetolol	Safe	IUGR
Atenolol	IUGR	IUGR (Lip et al, 1997)
Hydralazine	Safe	Fetal Thrombocytopenia, HELLP, ventricular arrythmias
$MgSO_4$		Neuromuscular blockade
ACE Inhibitors	?? Teratogenesis	IUGR, Renal Failure, PDA, Hypotension, IUFD

* Withdrawn in some countries due to hypotension in older age groups, not in pregnancy

Anti-hypertensives

- Lowering BP with antihypertensives can be life saving. 1st priority in severe hypertension.
- Oral therapy is usually sufficient for mild to moderate hypertension, if necessary
- National hypertension societies of the US, Canada and Australasia all list methyldopa, labetalol and nifedipine as acceptable.
- Methyldopa is an old drug, not often used outside of pregnancy. Difficult to obtain
- If a drug is unprofitable drug companies will withdraw it.

Oral Hyperglycemic agents



- The increased incidence of congenital anomalies in diabetes is related to poor control
- Better control is achieved with insulin than oral hypoglycemic agents. (De Swiet, 1979)
- Glyburide and metformin are effective, with no evidence of harm to the fetus (Moore et al, 2010)
- Women are given severe diets, rather than oral hypoglycemics.
- The fear of oral hypoglycemics was not due to teratogenicity, but lack of experience & therefore fear by Obstetricians.

Steroids

- In 1950s, reports on animal & human studies suggesting increased risk of oral clefts.
- Park-Wyllie (2000) in meta-analysis described OR of 3.4 (CI 2.0-5.7) for cleft lip with or without cleft palate
- Danish cohort study of 832,636 live births from 1996 to 2008: exposure to any steroids in 1st trimester **not** associated with increased risk for cleft lip or palate (Hviid et al, 2011)
- Bay Bjørn et al, (2014) assessed primiparous births from 1999 to 2009 (n = 83,043) OR, 0.4 (CI, 0.1-2.8).
- Clinical benefit of adequate Rx in 1st trimester for AID may far outweigh any small risk for oral clefts.

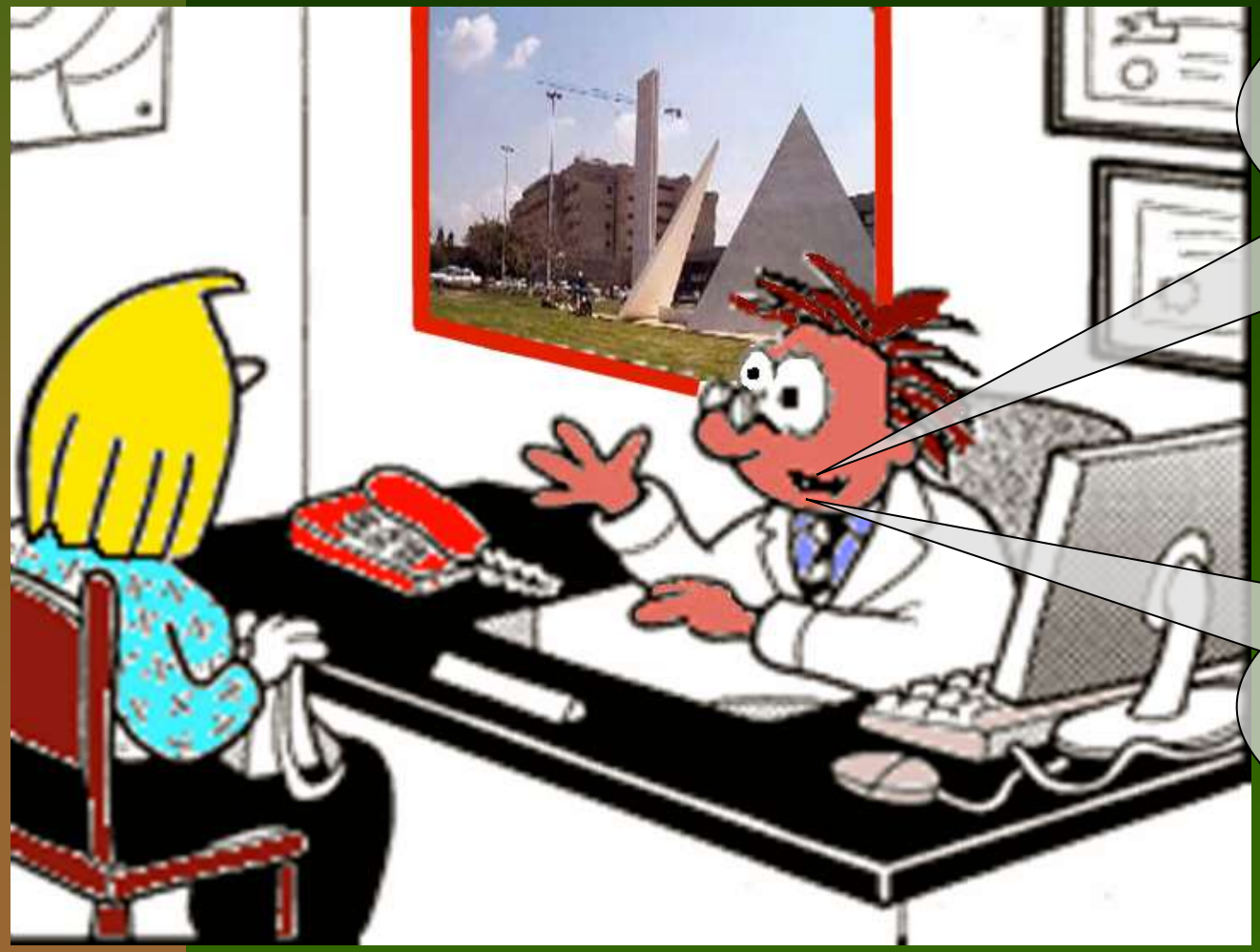
Dental Treatment

- Preiodontitis associated with pre-term labour
- However, dentists are often scared to prescribe antibiotics.
- Most common antibiotics in dental use are penicillins.
- Penicillins are completely safe.
- Why should women suffer dental disease in pregnancy?

Committees

- In some countries, committees have to approve abortion
- In U.K. – 2 physicians
- Committee members have been threatened
- Artificial abortions are approved, with no medical reasons

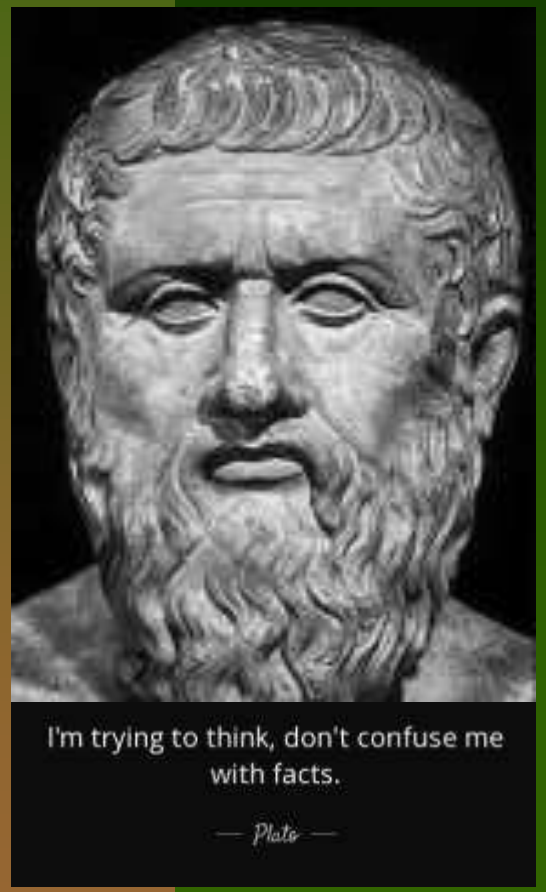
What to do?


We may or may not agree with abortion
But, we should tell the patient the truth

Where Are We Going?

- We must balance risk/benefit.
- Big data is available from HMO databases & global registers to determine risk
- Information is available after exposure & for consultation before prescribing.
- Consultation centres are available to advise on risks according to large databases.
- However, big databases must respect individual patients privacy.

Conclusions



- Drug companies are scared to develop drugs for use in pregnancy
- No improved drugs developed, drug pool will not expand as in other disciplines
- Older drugs will become harder to obtain, as not used outside of pregnancy, therefore not economic
- Women should not suffer unduly in pregnancy because of irrational fear.
- Risk must be balanced with benefit
- However, there will always be some residual risk.

Dydrogesterone

- Register, drawn up after literature search in September 2010 for all papers in EMBASE & MEDLINE, using terms, ‘Duphaston’ or ‘dydrogesterone’, reports were limited to clinical human data.
  - Luteal Phase Support, (9 studies, 152 patients); (Balasch, 1982; 1983;1986; Vanrell, 1980; Malik, 2000; Gelle, 1965; Sureau, 1964; Taubert, 1969; Vague, 1962) No cases of congenital malformations reported.
  - Threatened Miscarriage, (22 studies, 1380 patients) (Czajkowski, 2007; Ehrenskjöld, 1967; Mistò, 1967; El-Zibdeh, 2009; Omar, 2005; Pandian, 2009; Vincze, 2006; Bashmakova 2004; Vinokurova, 2009 ;Kalinka, 2005; Kalinka, 2006; Manukhin, 2004; Pelinescu-Onciul, 2007; Eggimann, 1979; Yamamoto, 1968; Chang, 1962; Gronow, 1985; Ketkar, 2008; Aydar, 1964; Backer, 1962; Gellé, 1965; Jamain, 1969; Sureau, 1964) No difference in anomalies in treated patients compared to controls (El-Zibdeh and Yousef, 2009; Eggiman, 1979)
  - Recurrent Miscarriage (10 studies, 99 patients) (El-Zibdeh, 2005; Freedman, 1970; Balasch, 1986; Chang, 1962; López-López, 1988; Aydar, 1964; Backer, 1962; Gellé, 1965; Jamain, 1969; Sureau, 1964) No difference in anomalies compared to controls (El-Zibdeh, 2005)