MENSTRUAL CYCLE

- The average age of menarche in humans is 12–13 years, but is normal anywhere between ages 8 and 16.
- The cessation of menstrual cycles at the end of a woman's reproductive period is termed **menopause**. The average age of menopause in women is 52 years, with anywhere between 45 and 55 being common. Menopause before age 45 is considered *premature* in industrialised countries
- The length of a woman's menstrual cycle will typically vary, with some shorter cycles and some longer cycles.
- A woman who experiences variations of less than eight days between her longest cycles and shortest cycles is considered to have **regular menstrual cycles**.
- Length variation between eight and 20 days is considered as **moderately irregular cycles.**
- Variation of 21 days or more between a woman's shortest and longest cycle lengths is considered **very irregular**

- The menstrual cycle can be described by the ovarian or uterine cycle. The ovarian cycle describes changes that occur in the **follicles** of the ovary whereas the uterine cycle describes changes in the **endometrial lining** of the uterus.
- Both cycles can be divided into three phases.

The ovarian cycle consists of the

- follicular phase,
- ovulation, and
- the luteal phase

The uterine cycle consists of

- menstruation,
- proliferative phase, and
- secretory phase.

Ovarian cycle

Follicular phase

- The follicular phase is the first part of the ovarian cycle. During this phase, the ovarian follicles mature and ready to release an egg. The latter part of this phase overlaps with the proliferative phase of the uterine cycle.
- Through the influence of a rise in **follicle stimulating hormone** (FSH) during the first days of the cycle, a few ovarian follicles are stimulated.
- Under the influence of several hormones, all but one of these follicles will stop growing, while one dominant follicle in the ovary will continue to maturity.
- The follicle that reaches maturity is called a **tertiary, or Graafian**, follicle, and it contains the ovum

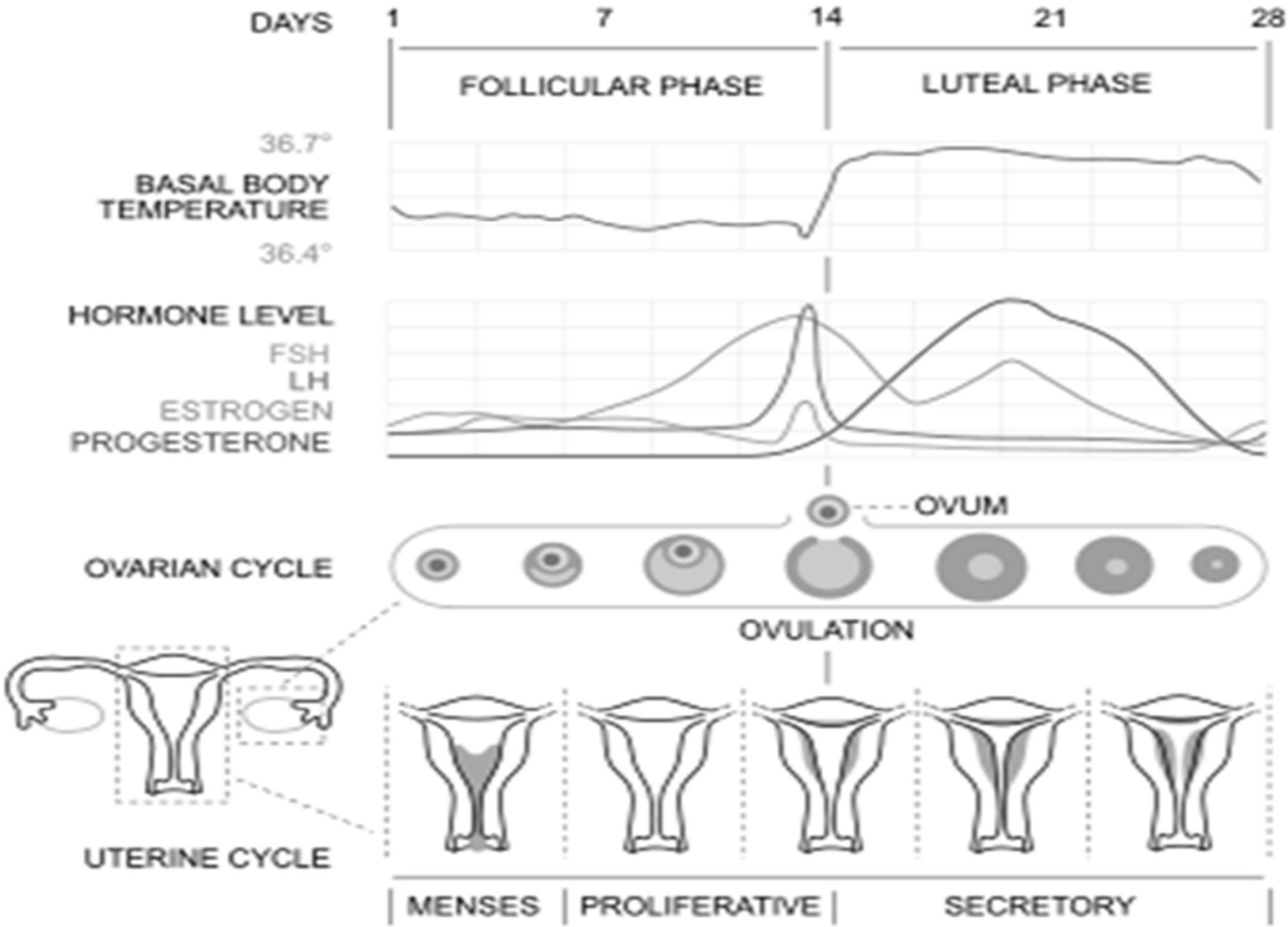
Ovulation

- Ovulation is the second phase of the ovarian cycle in which a mature egg is released from the ovarian follicles into the oviduct.
- During the follicular phase, estradiol suppresses production of luteinizing hormone (LH) from the anterior pituitary gland.
- When the egg has nearly matured, levels of estradiol reach a threshold above which this effect is reversed and estrogen actually stimulates the production of a large amount of LH. This process, known as the **LH surge**, starts around day **12 of the average cycle and may last 48 hours.**

Luteal phase

- The luteal phase is the final phase of the ovarian cycle and it corresponds to the secretory phase of the uterine cycle. During the luteal phase, the pituitary hormones FSH and LH cause the remaining parts of the dominant follicle to transform into the corpus luteum, which produces progesterone.
- The increased progesterone in the adrenals starts to induce the production of estrogen. The hormones produced by the corpus luteum also suppress production of the FSH and LH that the corpus luteum needs to maintain itself.

- Falling levels of progesterone trigger menstruation and the beginning of the next cycle. The loss of the corpus luteum is prevented by fertilization of the egg.
- If fertilization occurred the placenta, produces human chorionic gonadotropin (hCG), which is very similar to LH and which preserves the corpus luteum.
- The corpus luteum can then continue to secrete progesterone to maintain the pregnancy.


DAYS
1
7
14
21
28
FOLLICULAR PHASE
LUTEAL PHASE
36.7°
BASAL BODY TEMPERATURE
36.4°
HORMONE LEVEL
FSH
LH
ESTROGEN
PROGESTERONE
OVUM
OVARIAN CYCLE
OVULATION
UTERINE CYCLE
MENSES
PROLIFERATIVE
SECRETORY

- **Parity: is the number of live birth at any age or stillbirth after 24 weeks of** gestation.
- **Nullipara: describes a woman who has never delivered a fetus or fetuses beyond** 20 weeks of gestation.
- **Multipara: describes a woman who has had two or more deliveries past 20 weeks** of pregnancy.
- **Gravida: is the total number of pregnancies regardless of how they ended** (abortion, ectopic, normal pregnancy, hydatiform mole).
- **Nullgravida: a woman who has never been pregnant.**
- **Primigravidra: a woman who has been pregnant once.**

e.g. a woman who has had two spontaneous abortions and three normal intrauterine pregnancies may be described as **G5 P3 A2**

Dysmenorrhea (**dysmenorrhoea** or **painful periods**)

- Is a medical condition of **pain during menstruation** that interferes with daily activities
- ***Menstrual pain*** is often used synonymously with **menstrual cramps**, but the latter may also refer to menstrual **uterine contractions**, which are generally of higher strength, duration and frequency than in the rest of the menstrual cycle.
- Dysmenorrhea can feature different kinds of pain, including sharp, throbbing, dull, nauseating, burning, or shooting pain.
- Dysmenorrhea may precede menstruation by several days or may accompany it, and it usually subsides as menstruation tapers off. Dysmenorrhea may coexist with excessively heavy blood loss, known as ***menorrhagia***

Signs and symptoms

- The main symptom of dysmenorrhea is pain concentrated in the lower abdomen, It is also commonly felt in the right or left abdomen. It may radiate to the thighs and lower back.
- Symptoms often co-occurring with menstrual pain include nausea and vomiting, diarrhea or constipation, headache, dizziness, disorientation, hypersensitivity to sound, light,
- Symptoms of dysmenorrhea often begin immediately following ovulation and can last until the end of menstruation. This is because dysmenorrhea is often associated with changes in hormonal levels in the body that occur with ovulation.
- Dysmenorrhea can be classified as either **primary or secondary** based on the absence or presence of an underlying cause. Secondary dysmenorrhea is dysmenorrhea which is associated with an existing condition.

Causes of secondary dysmenorrhea

- The most common causes of secondary dysmenorrhea are
  - endometriosis,
  - ovarian cysts, and
  - pelvic congestion.

Management

Non-steroidal anti-inflammatory drugs (NSAIDs)

- **NSAIDs** are effective in relieving the pain of primary dysmenorrhea.
- They can have side effects of nausea, dyspepsia, peptic ulcer, and diarrhea.
- People who are unable to take the more common NSAIDs may be prescribed a COX-2 inhibitor.

Hormonal contraceptives

- **hormonal contraception** can improve or relieve symptoms of primary dysmenorrhea,

Other

- A review indicated the effectiveness of use of transdermal nitroglycerin.
- A number of alternative therapies have been studied in the treatment of dysmenorrhea.
  - behavioral interventions,
  - thiamine,
  - vitamin E,
  - fish oil,
  - vitamin B12

Amenorrhoea

- is the absence of a menstrual period in a woman of reproductive age.
- Physiological states of amenorrhoea are seen during pregnancy , lactation (breastfeeding), menopause and using contraceptive.
- Amenorrhoea is a symptom with many potential causes.

Primary amenorrhoea (menstruation cycles never starting) may be caused by developmental problems such as the congenital absence of the uterus, failure of the ovary to receive or maintain egg cells, and genetic diseases such as 5-alpha-reductase deficiency, delay in pubertal development will lead to primary amenorrhoea.

It is defined as an absence of secondary sexual characteristics by age 14 with no menarche or normal secondary sexual characteristics but no menarche by 16 years of age.

Secondary amenorrhoea (menstruation cycles ceasing) is often caused by hormonal disturbances from the hypothalamus and the pituitary gland, from premature menopause or intrauterine scar formation.

It is defined as the absence of menses for three months in a woman with previously normal menstruation or nine months for women with a history of oligomenorrhoea

Oligomenorrhea

- Is infrequent (or, in occasional usage, very light) menstruation. More strictly, it is menstrual periods occurring at intervals of greater than 35 days, with only four to nine periods in a year.

- **Oligomenorrhea can be a result of:**
  - Prolactinomas (adenomas of the anterior pituitary)
  - Thyrotoxicosis,
  - Hormonal changes in perimenopause, and Graves disease.
  - Polycystic ovary syndrome (PCOS)
  - Eating disorders can also result in oligomenorrhea. Although menstrual disorders are most strongly associated with Anorexia nervosa,

Drugs in Pregnancy and lactation

Pregnancy stages

- The human gestation period is approximately 40 weeks from the last menstrual period (38 weeks post conception) and is conventionally divided into the **first, second and third trimesters**, each **lasting 3 calendar months**.
- Another method for classifying the stage of pregnancy is according to the stage of fetal development. This is a more useful approach when assessing drug safety in pregnancy.

1-**The pre-embryonic stage** is the first 17 days post conception and involves implantation of the fertilized ovum.

2-**The embryonic stage** (days 18-56) is when the major organ system are formed.

3-**The fetal stage** (weeks 8-38) involves maturation, development and growth.

Signs and symptoms associated with pregnancy:

The signs of pregnancy can vary. Early signs can include nausea, breast tenderness, frequent urination, fatigue and headaches. Later signs can include heartburn, backache, constipation and fatigue.

- **Nausea and vomiting: Nausea predominantly affects women during the first three** months of pregnancy. Hormonal changes are an attributing factor.
- **Increased need to urinate: An increased need to urinate occurs early on as well as** during the last few weeks of pregnancy when it is caused by the increased pressure on the bladder from the uterus.

- **Headache: Headache occurs more frequently in pregnancy.**
- **Feeling hot and sweaty because of increased cardiac output and peripheral** vasodilation.
- **Dizziness and fainting.**
- **Fatigue.**
- **Epistaxis: Epistaxis (nose bleeding) is more common in pregnancy,**
- **Hypertension and pre-eclampsia.**
- **Thromboembolism: Thromboembolism is six times more likely in pregnancy**
- **Oedema: Oedema is common in normal pregnancies, affecting more than 80 per**cent of women.
- **Breathlessness.**
- **Heartburn: Heartburn is particularly common in the later stages of pregnancy.**

- **Appetite and weight gain: In the early stages, appetite may be lost but the** majority of pregnant women will experience increased appetite at some stage during their pregnancy. Weight gain averages around l2kg.
- **Constipation and haemorrhoids.**
- **Backache.**
- **Leg cramp is common in pregnancy, mostly at night.**
- **Hyperpigmentation and stretch marks**

Expected Date of Delivery ((EDD))

The EDD is calculated by **adding nine calendar months and seven days** (around 280 days in total) to the date of the first day of the last menstrual period (LMP).

The period from fertilization of the ovum to birth is given as 40 weeks from LMP

Some Commonly Used Abbreviations in Obstetrics

Abbreviations	Meanings	Abbreviations	Meanings
EDD	Expected Date of Delivery	FL	Fetal Life
FMP	First Missed Period	PT	Pregnancy Test
LMP	Last Menstrual Period	C/S	Caesarean Section
FM	Fetal Movement	NVD	Normal Vaginal Delivery
PCOS	Poly Cystic Ovary Syndrome	PUC	Premature Uterine Contractions
NTD	Neural Tube Defect	RDS	Respiratory Distress Syndrome

Considerations in pregnancy

Teratogenicity

A teratogen is an agent, e.g. drug, chemical or infectious disease, that interferes with the normal growth and development of the fetus.

Timing of drug exposure

- Some drugs can present a different risk according to the trimester of exposure. An example is **phenobarbital**, which can cause congenital anomalies if given in the first trimester and neonatal bleeding if given in the third trimester. In addition, there may be variable risk within a trimester. For example, folic acid antagonists, e.g. trimethoprim, would not be expected to cause neural tube defects if exposure occurred after neural tube closure, between the third and fourth week post conception.
- **Malformation** are thought to be unlikely unless the half-life of the drug is sufficient to extend exposure into the embryonic stage.
- **Organogenesis** occurs predominantly during the embryonic stage. Exposure to drugs during this period represents the greatest risk of major birth defects by interfering with organ formation.

Pregnancy Category A	Adequate and well-controlled human studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
Pregnancy Category B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.
Pregnancy Category C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Pregnancy Category D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Pregnancy Category X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Known Teratogens and Their Effects			
No	Drug class	Trimester of Risk	Comment
1	ACE-I and Angiotensin-II receptor antagonists	1,2,3	Potential teratogen: cause renal tubular dysplasia, skull hypoplasia & oligohydramnios.
2	Alcohol	1, 2	Regular use is teratogen (cause fetal alcohol syndrome)
3	Aminoglycoside	2,3	Potential damage of VIII cranial nerve (auditory) might cause hearing loss.
4	Amiodarone	2, 3	Complication reported: hypothyroidism & neonatal goitre.

5	Androgens	1, 2, 3	Masculinisation of female fetus
6	Benzodiazepine	1,2, 3	Avoid regular use might cause neonatal withdrawal syndrome, hypothermia & hypotonia.
7	Beta-blockers	2, 3	May cause intra-uterine growth restriction, neonatal hypoglycaemia, and bradycardia.
8	Carbamazepine	1, 3	Teratogen risk of neural tube defect (NTD) & risk of neonatal hemorrhage due to vitamin K deficiency.
9	Carbimazole	2, 3	Neonatal goitre and hypothyroidism, might cause fetal malformation
10	Chloroamphenicol	3	Neonatal gray syndrome
11	Iron (parenteral)	1	Avoid in first trimester.
12	Lithium	1,2,3	Congenital defect (tricuspid valve malformation).
13	NSAID	3	With regular use closure of fetal ductus arteriosus, pulmonary hypertension of newborn & delay duration of labor.
14	Methotrexate	1,2,3	Teratogenic.
15	Phenytoin	1,3	Congenital malformation (fetal hydantoin syndrome), vitamin K deficiency causing neonatal bleeding.
17	Quinolones	1,2,3	Avoid, erosion of cartilage and arthropathy
18	Statins	1,2,3	Avoid, congenital anomalies reported.
19	Sulfonylurea	3	Neonatal hypoglycemia.
20	Tetracycline	1,2,3	Affect skeletal development, result in permanent yellow-brown staining of teeth.
21	Valproic acid	1, 3	Risk of NTD, craniofacial anomalies.
22	VIT A High dose	1	Excessive doses (>25000U/day) may be Teratogen.
23	Warfarin	1, 2, 3	Teratogen, fetal and neonatal hemorrhage.

Pharmacokinetic changes

Volume of distribution: The weight gain of pregnancy is significant as a result of the fetus and an increase in total body water and fat. These factors increase the volume of distribution of drugs such that increased loading doses may be required.

Protein binding :Albumin is the main plasma protein responsible for binding acidic drugs such as phenytoin and salicylates, and α1-acid glycoprotein predominantly binds basic drugs, including ***B***-blockers and opioid analgesics. Plasma albumin concentrations fall significantly in pregnancy and this leads to an increase in the fraction of unbound drug. Clinical effect is related to the concentration of unbound drug, which usually remains unchanged even though the total (bound plus unbound) plasma concentration is decreased. Thus, a fall in the total plasma concentration does not usually require an increase in dose.

Clearance :Within the first few weeks of pregnancy the GFR increases by approximately 50% and remains raised until after delivery. Consequently, the clearance of drugs that are excreted unchanged mainly by the kidneys, e.g. lithium and some β-lactam antibiotics, is increased and higher maintenance doses may be required.

Drug selection

- Animal studies are not necessarily predictive of drug safety in human pregnancy, and there are species differences in the sensitivity to dysmorphogenic effects.
- In general, drugs that have been used extensively in pregnant women without apparent problems should be selected in preference to new drugs for which there is less experience of use. the benefits of drug treatment should outweigh any possible risk to the fetus.

Transfer of drugs into milk

- The transfer of drugs into milk is almost always by passive diffusion although drug transporters, e.g. organic cation/anion transporters, are increasingly recognized as playing a role.
- Milk differs from blood in that it has a **lower pH** and **less buffering capacity**, **lower protein-binding capacity** and **higher fat content**. Therefore, the following drug characteristics affect the extent of transfer.

1-pKa. For basic drugs a greater fraction will be ionized at an acidic pH so the milk phase will tend to 'trap' weak bases. In contrast, acidic drugs are more ionized at higher pH values and will tend to be 'trapped' in the maternal plasma.

2-Protein binding. Drugs that are highly bound to plasma proteins are likely to be relatively retained in maternal plasma because there is a lower total protein content in the milk.

3-Lipophilicity. Drugs that are highly lipophilic will dissolve into the lipid content of the milk, potentially increasing the extent of transfer from maternal plasma.

Milk to plasma concentration ratio

- The milk to plasma (M/P) ratio is often used as a measure of the extent of drug transfer into breast milk.
- Studies in humans demonstrate that most drugs have an M/P ratio less than 1.0, with the range of reported ratios being from around 0.1 to 5.0.
- It is often thought that drugs with high M/P ratios (e.g. 5.0) are unsafe because the concentration in milk exceeds that in plasma while those with low ratios (<1.0) are believed to be safe.

Table 47.6 Examples of drugs that give high infant exposure during lactation

Amiodarone
Carbimazole
Ethosuximide
Isoniazid
Lithium
Metronidazole
Phenobarbital
Theophylline
Propylthiouracil

Reducing infant exposure

A technique that is often recommended for reducing infant exposure is

1-**to give the maternal dose immediately after the infant has been fed** in an attempt to avoid feeding at the maximum milk concentration.

Other methods of helping to reduce infant exposure may be more readily achievable. These include

2-using topical treatments for local effect, e.g. short-term use of a corticosteroid cream for a minor skin complaint rather than oral antihistamines or steroids, and

3-avoiding large immediate oral/parenteral doses in favour of a longer course of a lower dose.