

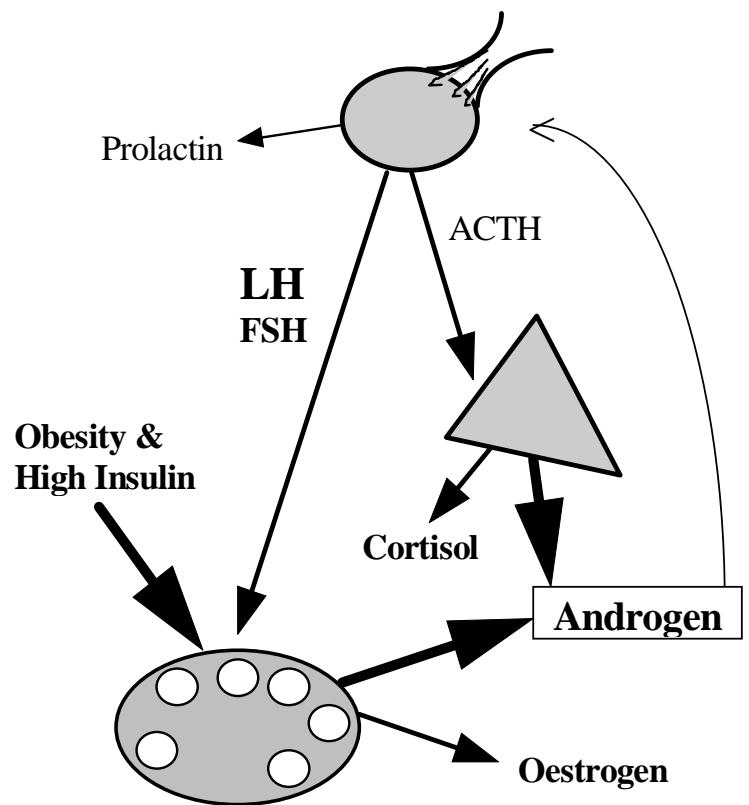
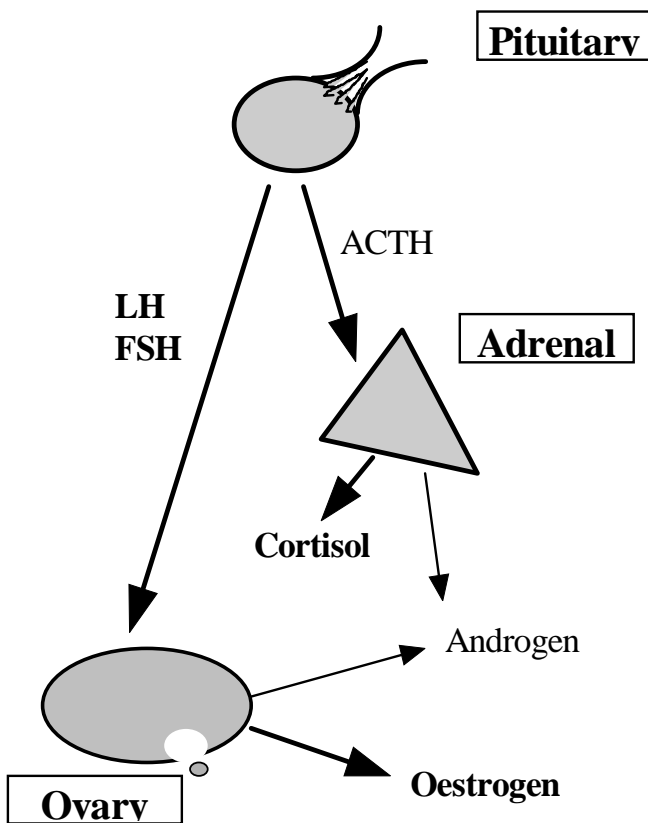
Polycystic Ovary Syndrome

PCOS (*Polycystic Ovary Syndrome*) is a common hormonal imbalance which may cause a variety of problems. People with this condition may complain of some, or all, of a number of symptoms including excess facial and body hair (hirsutism), irregular or absent periods, and difficulty becoming pregnant. Some, but not all, patients are also overweight.

PCOS is so-called because scans of the ovaries show that they contain many small cysts, a few mm in diameter around the edge of the ovary. This does *not* mean that you have an 'ovarian cyst' which is a completely different problem.

In fact, polycystic ovaries are just the most obvious part of an imbalance in the production of several normal hormones from the ovaries, adrenal glands & the pituitary gland, and levels of insulin in the body.

PCOS is very common. Surveys have shown that perhaps a quarter of normal women, including most of those with a mild excess of facial hair and many of those with slightly irregular periods, suffer from a mild version of the condition.



The Normal Hormone Balance:

The **pituitary gland** is connected to the underside of the brain and controls many other glands in the body by producing a variety of hormones.

The **adrenal gland** is mostly involved in producing the body's natural steroid hormone *cortisol*, under the control of the pituitary hormone *ACTH*

The **ovary** produces eggs for ovulation and produces the normal female hormone *oestrogen* under the control of the pituitary hormones *LH* and *FSH*

Both ovary and adrenal normally produce a small amount of male-like hormones, or *Androgens*.

In **PCOS**, both ovaries and adrenals produce rather more of the male-like *androgens* than normal. This is responsible for the excess hair growth and interferes with the normal cycle of ovulation and periods. Ultrasound scan may show multiple small cysts around the edge of the ovaries.

As a result of the changing balance of androgens in the blood the pattern of production of pituitary hormones is also altered (more LH than FSH, and sometimes more of another hormone prolactin). This in turn causes the production of even more ovarian androgen.

High **insulin** levels, made worse by obesity, also drive more androgens from the ovary, but a high insulin also makes it easier to gain and harder to lose weight. A vicious circle is therefore set up.

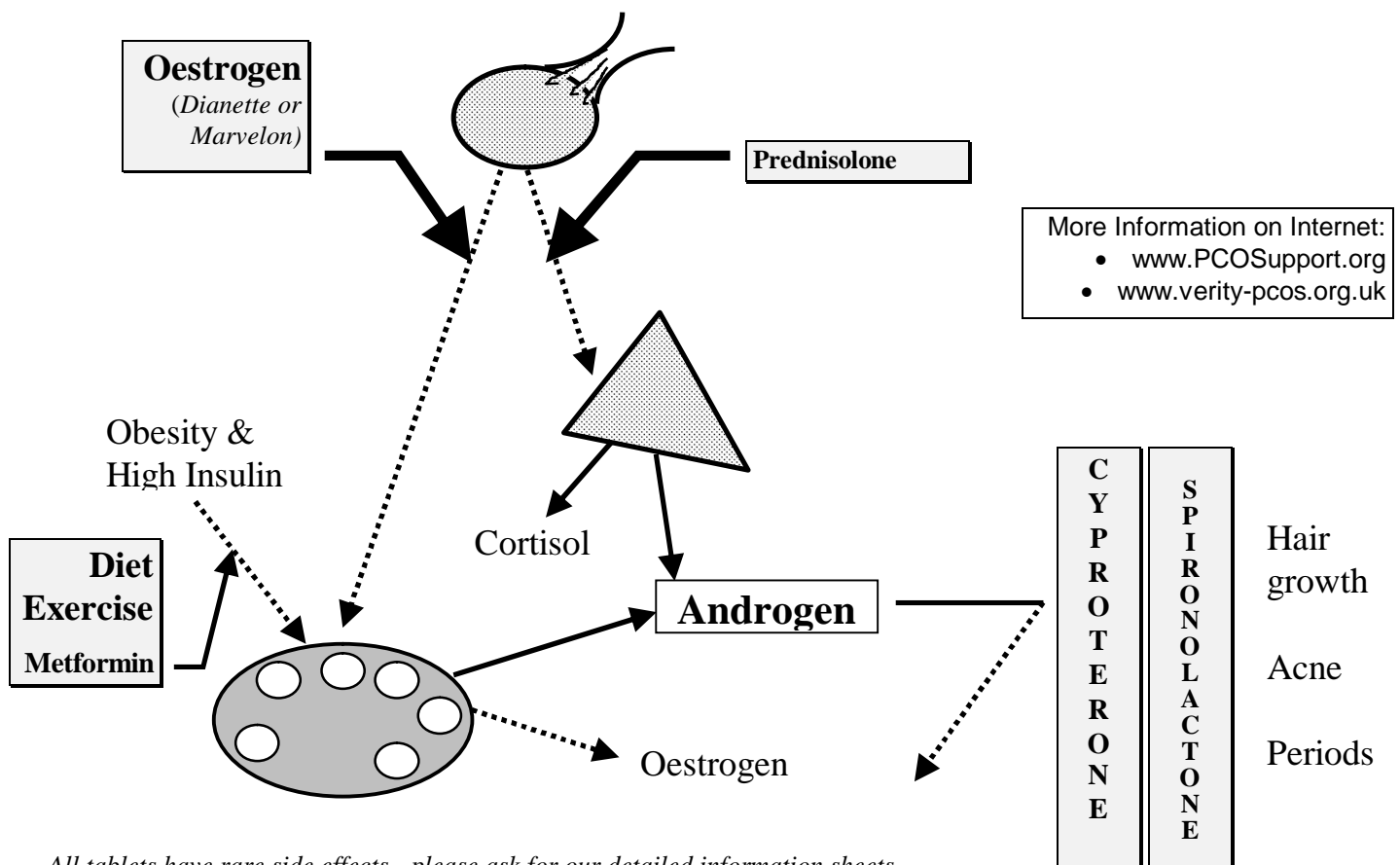
It is not clear whether this vicious circle begins with the ovary, the adrenal or even the pituitary or part of the brain which controls it. What is clear is that it represents a basic part of the way your body is built and handles its hormones and energy supplies.

Treatment of Polycystic Ovary Syndrome

Dr Trevor Howlett, Leicester Royal Infirmary 2011

The various problems of PCOS can be treated in several different ways:

1. You can remove the excess hair in any way which you find convenient (plucking, waxing, threading, shaving, electrolysis, 'laser' [but beware this is expensive], removal creams etc). Removal will not itself make the hair worse – but most methods of removal won't usually stop it regrowing either.
2. Regular exercise, and appropriate diet if you are overweight, will help reduce high insulin levels in your body and reduce this part of the vicious circle.
3. Treatment with oestrogen (usually a combined contraceptive 'pill' such as *Dianette* [Co-cyprindiol] or *Marvelon*) will switch off the ovary's excess production of androgen and will usually ensure regular periods
4. In more severe or resistant cases: Male-hormone-blocking drugs such as *Cyproterone*, *Spirolactone* or *Finasteride* can block the effect of androgens on the skin.
5. *Metformin* may be used to increase sensitivity to insulin
6. Occasionally adrenal hormone production can be switched off using *Prednisolone* (a steroid hormone)
7. If infertility is a problem, a number of techniques may help you produce an egg. This includes metformin and prednisolone, as well as tablets of *Clomiphene* and injections of *hCG* and *FSH*. For more complicated treatments we would refer you to the Assisted Conception Unit for closer monitoring.



All tablets have rare side effects - please ask for our detailed information sheets

Excessive hair is usually slow to respond to treatment (remember it has also usually taken several years to develop, and has to stop getting worse before it can get better). It is unusual to notice any significant benefit in less than 6 months, and the maximum effect usually requires a year or two of treatment.

Although more complicated treatments can usually be stopped after a couple of years, many patients find they need to continue with some simple treatment (such as the 'pill') in the longer term if they wish to maintain the benefits of treatment

How to take Dianette [Co-cyprindiol] (or Marvelon) and Cyproterone in combination:

Week 1	Week 2	Week 3	Week 4	Week 5	etc etc
1	Days		21	28	1 >>
					1 >>
1	14				

Combined treatment is taken on a regular cycle
Repeating the pattern every 4 weeks
 A period will normally occur in the week off treatment

Marvelon or Dianette: Take for Days 1 to 21 of every 28 days

Cyproterone: Take for Days 1 to 14 of each Pill pack

Choice of Drugs Used in Polycystic Ovary Syndrome & other causes of Hirsutism and Possible Side Effects

Endocrinology Clinics, Leicester Royal Infirmary



- Drugs are frequently used to treat the symptoms of polycystic ovary syndrome, and in particular to treat the excessive growth of hair.
- Inevitably all drugs have some side effects, although these are usually rare. Overall we know that all the drugs we might recommend for treatment of this condition are usually effective, and completely safe in the vast majority of people who take them, but this information sheet is designed to explain more fully the effects and possible rare side effects of these tablets.
- Drugs for PCOS usually need to be taken for many months or years and this means that a small number of people may suffer long term bad effects on their health due to side effects. If we were treating some other serious medical condition, then this small 'bad-health' effect would be balanced against a large 'good-health' effect in everyone else. However, when treating PCOS or other causes of excessive hair we are usually treating a symptom (often just excessive hair growth) which will *not* in itself have any bad effects on your long-term health.
- You should also be aware that none of the drugs we use routinely actually have an official drug license to treat excessive hair problems (although they are used for this throughout the world). In every case the official license has been given to treat some other condition.
- Because of this, we believe that it is important for every patient to understand the effects, and possible side effects, of the drugs used to treat PCOS, and to be happy in her own mind that the problem being treated (and the good effect usually obtained) is 'worth' the very small risk of side effects due to the drug.

Suppression of the Ovaries using the Combined Oral Contraceptive

This is the most common treatment used to treat hair and period problems. It 'switches off' the ovary from producing its abnormal hormone levels and usually enforces a regular period cycle. Good effects on hair growth occur in most people after 6-12 months and then continue to improve for several years on treatment.

- All such 'Pills' may cause minor symptoms - such as fluid retention, slight weight gain, and changes in mood - in people who are sensitive to them.
- Migraine and high blood pressure may both be worsened, and these conditions often mean that the 'Pill' cannot be used. If you have 'hemiplegic' migraine with weakness or numbness of one side of the body during the migraine aura then you must not take the Pill (increased stroke risk)
- Patients often worry about cancer, but the news here is good - cancers of the ovary and body of the womb are much *less* common in women on the pill; cancer of the neck of the womb (cervix) is more common but this may actually be related to sex rather than the Pill itself, and in any case is picked up and treated by the cervical smear screening programme. People worry about breast cancer but the most complete study so far has concluded that the risk of breast cancer is only increased by 1% in women on the Pill, and decreases back to normal when Pill is stopped
- Risk of blood clots is the most significant problem to consider. This is a particular problem in women who are over 35 years old and who smoke or are very overweight, and we usually avoid the Pill in these women. Blood clots in the legs (which cause sudden onset of a red, painful, swollen leg) occur rarely but we now know that Pills which tend to have the best effect on hair have a slightly higher risk of blood clots compared to older Pills...

Marvelon - is a 'modern' Pill which we know improves hair problems in a majority of women. It contains a low dose of oestrogen (30 micrograms) and a newer 'progestagen' which has no male-like activity.

Yasmin is a similar modern Pill. **Dianette** (also known as **Co-cyprindiol**) - contains a slightly higher dose of oestrogen (35 micrograms) and a small dose of an 'anti-male' hormone - cyproterone - and has been most widely used around the world. These types of Pill are now known to have a slightly higher risk of blood clots in the leg than older pills. The risk for Marvelon has been estimated as 30 per every 100,000 years taking the drug (compared to 5 per 100,000 on no treatment) - so that the absolute risk is actually very small - but about twice the risk of older 'Pills' (see below). The risk for Dianette appears to be similar. Only a minority of people who develop a blood clot would go on to get one of the more serious complications which threaten life (e.g. a pulmonary embolism). The risk of dying due to this sort of Pill has been guessed to be one in 500,000 years (which is rather less than the risk of being murdered, and

compares to a risk of dying from smoking cigarettes of 1 in 200 per year). In addition, for Dianette, rare serious side effects have been described in men taking higher doses of cyproterone (see below), but this has rarely if ever been seen on the sort of doses found in Dianette. We know that both of these Pills help hair growth, but no one has ever proven whether one is better than the other. We tend to use Dianette in the first instance since we often wish to add a higher dose of cyproterone later on. There is also a recent suggestion (as yet unproven) that Dianette may worsen depression.

Other 'Pills' - are exactly the same as Dianette or Marvelon in all side effects apart from blood clots. Older Pills (e.g. Microgynon 30, Brevinor) are now known to have a slightly lower risk of blood clots (quoted as 15 per 100,000 years) and so are preferred if the only aim is contraception or making the periods regular. However, these older pills all contain a progestagen with mild 'male-like' actions, which means that they are usually not effective in helping excessive hair or acne. These Pills cannot therefore be recommended to treat this sort of problem.

Cyproterone Acetate

Cyproterone is a drug which blocks the action of male-like hormones. It is usually our second line drug if Dianette alone has had no effect on hair problems after 6-12 months.

- Cyproterone is almost always used in combination with a contraceptive pill, usually 100mg taken for the first 14 days of every Pill pack. This is used because ...
 1. This combination appears to be the most effective for improving excessive hair
 2. Cyproterone is long acting and usually stops the periods completely if given alone
 3. Since the drug would block the male hormones of a male baby it is essential that pregnancy is avoided
- Cyproterone usually makes the periods lighter and occur later in the week off the 'Pill'. Sometimes this means that the periods don't happen at all, and we then need to reduce the number of days of cyproterone treatment – typically to the first 12 days and then the first 10 days is still no periods. This is more likely in people who are very overweight
- A few people get a little drowsy or depressed on treatment - but this is not often a problem
- A rare serious side effect causing damage to the liver has been described. This is usually in men taking 200-300mg of cyproterone every day for prostate cancer, and it seems to be extremely rare (if it occurs at all) in women taking our normal dose. Because of this slight risk we will check your liver blood tests before and during treatment. You should stop treatment immediately if you become jaundiced (yellow skin/eyes)
- Cyproterone may encourage the growth of a type of benign brain tumour called meningioma – you should not take cyproterone if you are known to have this sort of tumour.

Spironolactone

Spironolactone is another drug which blocks male-like hormones. We normally use this in women who cannot take the Pill and/or Cyproterone. The usual dose is 200mg a day.

The drug was developed as a mild water tablet and has also been used to lower blood pressure (it also blocks another hormone in the kidney) - this may be another reason for choosing this drug.

Most people feel well on Spironolactone but potential problems include..

- Upset of the balance of salt and water in your body due to its water-tablet effects. We will check a blood test to rule this out.
- Periods may become more irregular, although many patients notice no change, and in some the periods actually seem to get better!
- Since the drug would block the male hormones of a male baby it is essential that pregnancy is avoided – which means additional care with contraception in many cases
- Bleeding stomach and duodenal ulcers may be more common (2-3x the very small normal risk)
- Substances derived from spironolactone *may* cause tumours in *rats* when given in high doses for a long time. This effect has never been proven in human beings, but has led the drug licensing authorities in this country (but not in most other countries) to suggest that it should not be the first-choice when someone needs a water tablet. There is no proof that this is a real risk, but not enough information to completely rule out this problem as a rare side effect – although it seems unlikely to be significant for short to medium term use. If you are taking this drug long term, then you need to be happy in your own mind that the benefit you are getting from treatment is sufficient to justify with small theoretical risk.

Choice of Drugs Used in Polycystic Ovary Syndrome & other causes of Hirsutism and Possible Side Effects:

2) Newer or Less common Drugs

Endocrinology Clinics, Leicester Royal Infirmary



- Drugs are frequently used to treat the symptoms of polycystic ovary syndrome, and in particular to treat the excessive growth of hair.
- Inevitably all drugs have some side effects, although these are usually rare. Overall we know that all the drugs we might recommend for treatment of this condition are usually effective, and completely safe in the vast majority of people who take them, but this information sheet is designed to explain more fully the effects and possible rare side effects of these tablets.
- Drugs for PCOS usually need to be taken for many months or years and this means that a small number of people may suffer long term bad effects on their health due to side effects. If we were treating some other serious medical condition, then this small 'bad-health' effect would be balanced against a large 'good-health' effect in everyone else. However, when treating PCOS or other causes of excessive hair we are usually treating a symptom (often just excessive hair growth) which will *not* in itself have any bad effects on your long-term health.
- You should also be aware that none of the drugs we use routinely actually have an official drug license to treat excessive hair problems (although they are used for this throughout the world). In every case the official license has been given to treat some other condition.
- Because of this, I believe that it is important for every patient to understand the effects, and possible side effects, of the drugs used to treat PCOS, and to be happy in her own mind that the problem being treated (and the good effect usually obtained) is 'worth' the very small risk of side effects due to the drug.

Finasteride

Finasteride is a drug which blocks the production of a powerful male-like hormone in the skin itself. Like most anti-male-hormone drugs, it was developed for use in men with prostate problems - but has been used to treat excessive hair problems in women.

- Studies comparing different treatments suggest that addition of finasteride to the 'Pill' causes further improvement in excessive hair - but show that overall the effect is much the same as Cyproterone and Spironolactone (with which we have greater experience).
- *We may suggest finasteride in patients who cannot tolerate cyproterone or spironolactone, or in whom these drugs have not been effective.*
- Since the drug would block the male hormones of a male baby it is essential that pregnancy is avoided (which is also why the drug pack information insert says that women should avoid it)
- There is little published long-term experience of finasteride or its side effects in women, but in men relatively few side effects have been described. Patients are sometimes allergic to the tablets, which may cause lip swelling and rash - if this occurs you should stop the treatment.
- There is a drug safety warning about a possible (but not proven) increase in male breast cancer in men taking this drug – the significance of this possible risk for women taking the drug is unknown.

Metformin

Metformin is a drug which has now been used for over 15 years in the treatment of PCOS, but which has been used from very many years in the treatment of diabetes. It works by increasing the sensitivity of the body to insulin - women with PCOS are often 'insulin resistant', and we now know that this resistance contributes to the hormonal imbalance which causes the symptoms of PCOS.

- Several studies have suggested that metformin improves the irregularity of the periods, increases the chance of ovulation ('releasing an egg') and therefore increases the chance of falling pregnant in PCOS – particularly when overweight.
- For fertility it is probably less powerful than some other drugs (clomiphene) – but equally it can be given more simply and used for longer.

- Metformin is less effective in helping the excessive hair growth, although it does appear to help in a significant proportion of cases.
- You may have heard the metformin helps weight loss. This certainly seems to be true for some people but it seems not for everyone and, although the effect can occasionally be dramatic. For most people it is only a matter of a few pounds.
- Metformin can cause stomach upsets (nausea, vomiting, diarrhoea) so that we recommend that the dose is slowly increased to the usual dose of 1 tablet (500mg) three times a day over a couple of weeks and taken with the main meals - if this is done then most people can take the tablet without problems. If you are unable to take ordinary metformin due to these side effects then we usually recommend changing to the 'slow-release' form of the medication in the same dose and regime.
- Metformin is not recommended in people with liver or kidney problems, and we will check this before starting the drug. Metformin is not usually recommended in pregnancy in diabetics (since insulin treatment is always recommended in such cases in the UK), but even in diabetes has been used without problems in some parts of the world. In PCOS there is still inconclusive information to suggest a benefit, but no evidence of harm, in patients who become pregnant - however it is sensible to stop the drug as soon as pregnancy is confirmed. The only exception to this is if there have previously been multiple miscarriages – when we occasionally recommend continuing the drug.
- Overall, in our experience, metformin seems to be a great help to some people, but doesn't help everyone.
- *We often suggest use of metformin in our clinic in patients who are overweight, especially with irregular periods and/or trying to fall pregnant.*

Clomiphene

Clomiphene is used to stimulate the ovaries to produce eggs and is usually the next step if someone is having difficulty becoming pregnant. This is usually supervised by the Fertility clinic. The usual dose is 50mg-100mg from days 2 to 6 of the menstrual cycle.

- Clomiphene rarely causes disturbances of vision (the drug should be stopped)
- The risk of multiple pregnancy is slightly increased, but anything more than twins is very rare
- If the ovaries are over-stimulated then they may become swollen and painful - contact your doctor if you get severe pain in the lower part of your abdomen.
- The Committee on Safety of Medicines has warned that there might be an increased chance of ovarian cancer if the drug is used for a long time and have recommended no more than 6 cycles of treatment (but this needs to be balanced against the fact that becoming pregnant considerably *reduces* your risk of ovarian cancer)

Steroid Hormones

Steroid hormones (Prednisolone or Dexamethasone) improve the hormone imbalance of PCOS. They do not seem to have very much effect on the hair problems, but can improve acne, make the periods more regular and help fertility.

- Giving more steroid hormone than the body usually produces would cause a large number of side effects - and you may well read about these. However, these are only seen with doses much higher than those we would recommend for PCOS
- We aim to give the same dose of steroid which your body normally makes, and give it in a special way to switch off your natural steroid hormones and 'swap one for the other'. It is hard to get this dosage perfect, so steroids are rarely used as a long-term treatment, but may occasionally be helpful.
- If we use these drugs, you should carry a steroid card and will need to increase the dose if you suffer from another stressful illness (e.g. diarrhoea or 'flu'). Be sure that you have a copy of our 'Steroid replacement' information sheet if you are taking these tablets