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## *Personal practice*

# Turner syndrome

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In 1932 Dr Henry Turner examined a 16 year old girl who was 134·5 cm tall and lacked breast and sexual hair development. She was noted to have neck webbing, a low hairline, and an abnormal carrying angle of the elbow. The epiphyses of the bones of the hands and the wrists were still open. After treatment with oestrogen was begun, breast and pubic hair development occurred and a small uterus was palpated. The addition of a progestational agent to the treatment protocol resulted in the patient experiencing her first menstrual period. When the patient was re-examined at the age of 60 in April 1975, her height was 148 cm, and she had had no menstrual periods since her hormonal treatment was stopped at the age of 22.

Many would aver that we have advanced little since the original description and management of this patient by Dr Turner. Most conduct treatment as he did but, in the light of recent understanding of some of the pathophysiology of the condition, there are some improvements in management that are now available.

### Pathophysiology

Most patients have a single X chromosome, but other abnormalities of the X chromosome have been defined, and mosaic karyotypes, including the presence of Y chromosomal material, are common. The clinical features are similar and short stature is the hallmark of the condition.[1]

In patients with the Turner syndrome the ovary forms normally but becomes progressively atretic. In normal women the number of ova rises rapidly to reach a peak of around seven million ova at 7 months' gestation and then falls away during childhood and reproductive life.[2] In the Turner syndrome the rate of decay is accelerated so that the patient effectively becomes menopausal before she reaches puberty. This is not invariable, and there are patients who develop secondary sexual characteristics and then experience a premature menopause. In some cases, in whom ovarian decay was presumably not complete until an older age, pregnancy has been documented.

### Growth in the Turner syndrome

Patients with the Turner syndrome are born short. Growth velocity in the preschool years is usually around 50th centile and falls progressively to follow 10th centile velocity during the primary school years. The addition of successive 10th centile velocities to an already fairly short child means that children with this condition become increasingly obviously short as the years go by. The mean final height of untreated patients with the Turner syndrome is about 142 cm, but the standard deviation about this mean height is similar to that in normal women—that is, 6 cm.

Children with the Turner syndrome maintain the same mid-parent child correlation for height as do normal children: in other words, the loss of the genetic material on the X chromosome leads to the removal of a constant amount of height from the genetically determined stature. The daughter of very tall parents may not, therefore, be obviously short until quite late in childhood.

In the untreated patient there is an additional lack of the growth that is normally associated with puberty. It is important to remember that the earlier puberty occurs the greater is the growth spurt, so there is no point in allowing a girl with the Turner syndrome to plod slowly on through her early teens in the mistaken belief that the late exhibition of oestrogen will bring a rapid improvement in growth rate, which can be added to growth that has already been achieved. The interaction of puberty and the attainment of final stature is one of the most important aspects of management.

The reason why children with the Turner syndrome grow badly is far from clear. It has recently been shown that girls with the Turner syndrome aged 2 to 8 had growth hormone profiles that did not

differ from aged matched controls.[3] By contrast, girls with the Turner syndrome aged 9 to 20 had significantly decreased growth hormone secretion compared with those in aged matched controls. Obviously, they could not be matched for puberty.

The transient growth hormone 'deficiency' of late prepuberty is well established, and we have recently shown that very small doses of sex steroids restore pulsatile growth hormone secretion in hypogonadotrophic hypogonadal children[4] and in those with simple delay of puberty.[5] We have also shown that the prepubertal ovaries of girls are anything but quiescent and that cycles of ovarian follicular development of low amplitude and long periodicity are characteristic of normal female development.[6] The lack of (normally very low) oestrogen secretion is probably responsible for the relative growth hormone deficiency of agonadal girls, which is why very low dose oestrogen replacement improves growth velocity.

**Clinical consequences of the diagnosis**

Osteoporosis is a feature of untreated patients with the Turner syndrome, and the radiographic occurrence of osteoporosis is a characteristic feature of patients diagnosed in the teenage years. The extent to which this may be avoided by earlier introduction of treatment with oestrogen has not been properly studied at the present time.

The malignant potential of the dysgenetic gonad is not great in patients who have a karyotype that does not contain Y chromosomal material.[7] A patient with gonadal dysgenesis who has a Y chromosomal component has a high risk for the development of a germ cell tumour, and the gonads should therefore be removed, even if they appear inconspicuous on ultrasound.

The risk of gonadal neoplasm increases with age and approaches more than 50% as the third decade is reached. In the past it was recommended that hysterectomy accompany gonadectomy as this would facilitate oestrogen replacement, but this view is out of date.

**Management**

The management of the Turner syndrome involves three stages; firstly, diagnosis and discussion, secondly, what to do about growth, and, thirdly, the induction of puberty. Obviously associated features such as coarctation and hypertension need treatment in their own right.

**Discussion with parents.** In most instances the diagnosis of gonadal dysgenesis should be made long before a patient is referred for lack of pubertal development. Often the diagnosis will be suspected in the newborn period, but more often it will become apparent as a result of the low growth velocity or the other abnormalities that are part of the phenotype. The diagnosis should be clinched by chromosome analysis and the situation then discussed with both parents. The discussion should cover the implications of the diagnosis, future management, and the implications for reproductive function. I devote a considerable amount of time to discussing with parents what they are going to say to their daughter.

The anxiety that most mothers have is to share with their daughters the knowledge that they will be infertile. In my experience, this is rarely a paramount issue for the child herself. Adolescents seem generally not to associate secondary sexual development with reproductive function. One can explain to a girl that she requires treatment with oestrogen because she has no ovarian function, and it seems not to occur to her that because she has no ovaries she will not be able to be pregnant. I therefore recommend mothers to take their fences one at a time and to start the education process slowly. Obviously, in a younger child the immediate problem is shortness of stature, and the treatments for that are not difficult to explain. When it comes to explaining about oestrogen replacement most girls take the necessity for treatment as a fairly straightforward matter. I have yet to experience a teenage patient who immediately associates oestrogen replacement with infertility.

It is also worth bearing in mind that in vitro fertilisation techniques can enable patients with the Turner syndrome to carry the child of their spouse, even if the egg was not obtained from themselves. Theoretically, it might be worth considering storing an ovum from an ovarian follicle in a patient with the Turner syndrome before the ovaries become atretic: this is not practicable at the present time and might be undesirable because of the potential for recovering ova with chromosomal abnormalities. It may become possible and, at worst, one would run the risk of implanting a fertilised egg that would have the same chromosomal constitution as the mother: a YO fetus would be aborted.

There is often a misapprehension about intelligence in patients with the Turner syndrome. The distribution curve of IQ is shifted a little lower than in the general population, but the overlap is such that an academic career is not precluded. This is obviously in pronounced contrast to some of the other sex chromosomal disabilities, such as Klinefelter's syndrome.

Generally speaking, therefore, although the initial discussion of the diagnosis is an unhappy

experience for most parents, the prospect that they will have a daughter who, although she may be short and may not be able to bear her own children, will be able to live a normal life in every other way is generally encouraging. I am in favour of parents joining the Turner Syndrome Society* because the Society has members of all ages who can be of considerable support both to the parents and to the patients.

**Management of growth.** Treatment of short stature comprises two elements, the short term and the long term. There are many treatments that can improve growth velocity in the short term. There is dispute about whether treatment with anabolic steroids and/or growth hormone associated with the early and phased introduction of oestrogens leads to taller ultimate stature.

Anabolic steroids have a long track record. Oxandrolone increases height velocity, although the mechanism by which this occurs is not understood either for this group of patients or for others. Preliminary data in our group suggests that it increases integrated growth hormone secretion over 24 hour periods by augmenting growth hormone pulses.[5] We regularly observe that oxandrolone given in a small dose (say 1·25 mg daily) to a patient whose growth velocity has fallen below 4·5 cm per year restores a normal growth velocity: sometimes catch up growth is induced during the first year of treatment and occasionally for longer than this. The long term results are difficult to assess because of the different doses that have been used in different published series.

As far as side effects are concerned, those on skeletal maturation have long been recognised to be dose related.[8] In the doses that I use height prediction has not been disadvantaged and in many publications has been improved.[9–11] In over 100 consecutive patients with various diagnoses we have observed no masculinising or other side effects. Other anabolic steroids, such as fluoxymesterone, have been used in the past, but these are no longer available.

The incidence of growth hormone deficiency seems to be greater in patients with the Turner syndrome than in a control population. It has become increasingly clear that what has been called growth hormone deficiency is just one end of the range of physiological growth hormone secretion.[12] We have clear evidence that the growth hormone profiles produced by short children growing normally are considerably diminished in terms of pulse amplitude compared with the growth hormone profiles produced by tall children. The profile of 'normal' short children clearly overlap with those of patients who have 'partial growth hormone deficiency' defined on the basis of a level of growth hormone achieved in a pharmacological test. Reliance on such tests may exclude many children who would benefit from growth hormone treatment. The data on growth hormone dynamics in older patients with the Turner syndrome suggest that many of them might respond to exogenously administered growth hormone—but so might many apparently normal small children.

In the case of normal small children, the effect of exogenously augmenting growth hormone remains sub judice, but there is increasing evidence that the addition of growth hormone to older patients with the Turner syndrome improves growth velocity in the short term and may well improve long term prospects for height.[13]

**Induction of puberty.** In all cases where puberty is to be induced, the object should be to keep the patient in line with the development of the peer group. Fifty per cent of normal girls show signs of pubertal development before their 12th birthday, and two years is a reasonable minimum time between the onset of puberty and menarche. Patients with the Turner syndrome should follow a similar time scale.

There are data that advocate the earlier introduction of preparations containing oestrogen to stimulate growth, although the amount of oestrogen must be kept very low. Oestrogens in large amounts inhibit growth, even though growth hormone secretion is very sensitive to oestrogen stimulation.[14] The reason for this paradox is that generation of the somatomedins by the liver and their action at the periphery are both inhibited by oestrogens. Physiological doses of oestradiol (less than 5 μg of ethinyloestradiol) given by mouth accelerate growth through augmenting growth hormone secretion, but double the dose may well inhibit growth. Growth promoting doses of ethinyloestradiol are much smaller than the amounts contained in the lowest dose oestrogen tablet on the market.

One complication of oral administration of ethinyloestradiol is that the drug is absorbed into the portal blood and the liver is exposed into a much larger amount than it lets pass into the systemic circulation. As oestradiol inhibits somatomedin generation, though it promotes growth hormone secretion, oral administration of oestrogen may be just what the patient with Turner syndrome does not need. Oestradiol from a normal ovary is not released into the hepatic portal circulation. In future, therefore, there may be some advantage in contemplating administration of oestrogens by a

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parenteral route. At the present time this has not been adequately researched, but one certainty is that most doctors have been accustomed to introducing much larger doses of ethinyloestradiol far quicker than is beneficial to the patients.

The practical regimen must therefore be to introduce *very* small (2 μg or possibly less) doses of ethinyloestradiol at an early age when the ovary of the normal girl is beginning to secrete oestrogen. Doses should then gradually be increased over long periods to induce puberty and eventually to bring about oestrogen withdrawal bleeds.

When puberty is complete it is wise to continue cyclical administration of oestrogen to prevent osteoporosis, to delay atherosclerotic cardiovascular disease, to maintain well developed secondary sexual characteristics, and, in the context of an active sex life, to enable intercourse to take place comfortably through the medium of a well oestrogenised vagina.

**A practical regimen**

At the time of writing my scheme for the medical management of the patient with Turner syndrome starts ideally with a patient in whom the diagnosis has been made early. Careful longitudinal measurements of growth are required and as soon as the velocity of growth over any one year falls below the 25th centile or 5 cm per year, whichever is the greater, I consider introducing a growth promoting regimen. This may be with oxandrolone in low dosage, with growth hormone, or, in the older patient, with very low doses of ethinyloestradiol. In any patient with the Turner syndrome who is growing at a rate of less than 4 cm per year serious consideration should be given to examining the dynamics of growth hormone secretion. It is not yet possible to advise whether augmenting growth hormone in a patient with the Turner syndrome who responds 'normally' to a pharmacological stimulus of growth hormome secretion or giving oxandrolone will produce the better long term result, and the results may be additive.[13] It seems that patients deserve the benefit of the doubt and should be given one or other agent.

Until growth hormone becomes available in large amounts oxandrolone may well be the first choice of treatment in a dose of 1·25 mg daily. This will produce a brisk increase of height velocity from about 4 cm per year to about 6 cm per year, and this is generally maintained for two years or so. When the height velocity begins to fall on this treatment it is my practice to add ethinyloestradiol 2 μg daily continuously to the therapeutic regimen. This results in a further increase in height velocity, and as long as this is maintained I am inclined to leave patients on this treatment. While there may be theoretical dangers of unopposed treatment with oestrogen in older patients, the fact is that normal prepubertal girls get a substantial amount of oestradiol from their ovaries without any progestogen, and thus it seems unlikely that this therapeutic regimen will prove hazardous. Obviously, as in all patients being treated with oestrogen, blood pressure must be monitored regularly.

At the age when puberty usually occurs the height velocity begins to fall again, and I then increase the dose of ethinyloestradiol to 5 μg daily continuously for a minimum of six months and sometimes longer, according to age and clinical circumstances. I then increase the dose to 10 μg daily for at least the same time. Larger doses on a shorter time scale should not be employed because this causes nipple and areolar development without adequate underlying breast development.

At the age of 14 years, assuming that induction of puberty was begun during the 11th or 12th years of life, or if there is breakthrough bleeding on the oestrogen regimen being employed, a progestogen should be given in addition to ethinyloestradiol. Certainly, any patient who is to receive more than 10 μg of ethinyloestradiol daily needs a progestogen as well to prevent breakthrough bleeding. Alternative drugs are norethisterone 350 μg or levonorgestrel 30 μg, and these will be given with the oestrogen for one week in four. When 20 μg of ethinyloestradiol is being given, there is a combined pill (Loestrin 20) that is not favoured by specialists in the field of contraception because it contains a very large amount of progestogen (norethisterone acetate 1 mg). On the other hand, they are pressed to provide a reason not to favour this drug for its convenience as far as the patient with Turner syndrome is concerned. The alternative is to provide two drugs, the oestrogen continuously and the progestogen added for one week out of four. I favour the combined pill.

If breakthrough bleeding occurs on a low dose of ethinyloestradiol, norethisterone acetate 5 mg should be given daily for one week before stopping everything for a week before commencing combined drugs. Ultimately, it is necessary to go on to one of the combined replacement tablets that contain 30 μg ethinyloestradiol daily. There seems little to choose between the many varieties on the market, but I favour Brevinor or Ovysmen for combined preparations and Logynon or Trinordiol phased formulations.

The aim of these regimens is to keep a patient as nearly as possible in line with her peer group and to maximise her chances of ultimate stature. In gen-

eral, there are satisfactory cosmetic results, although some patients, even with a slow introduction of oestrogen, do not have breast development that they consider adequate. In such cases, I do not hesitate to make referral to a plastic surgeon for consideration of augmentation mammoplasty. Plastic surgery may also have a part to play if neck webbing is a serious problem but in my experience many patients with the Turner syndrome tend to develop keloid scars, and such intervention must be very carefully discussed for that reason.

## Conclusion

The patient with the Turner syndrome presents a considerable clinical challenge. Because few patients are seen by any one physician, few physicians have much expertise in the management of the condition. It is my contention that most girls with the Turner syndrome can be afforded a better ultimate prognosis than many are currently enjoying through the judicious use of the agents that I have mentioned. They can certainly be enabled to think that they are not different from other girls of their age, and this in itself must be one of the most important psychological advantages they may enjoy.

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