Intersex surgery in the adult

C.R.J. WOODHOUSE
The Institute of Urology and Nephrology, University College London, and The Hospital for Children, Great Ormond Street, London, UK

INTRODUCTION

The study of individuals born with ambiguous genitalia is undergoing a revolution. In the past the birth of such a baby was regarded as a medical emergency. The management was based on defining the diagnosis as closely as possible, choosing the most 'appropriate' gender and persisting with it. Most children were never told of their original diagnosis, especially if the gender chosen was different from their genotype.

The criteria for assigning gender are strongly dependent on local culture. This effect has been particularly studied in the multicultural nation of Malaya. Amongst Muslim Malays, women can have a prominent role in public life, inherit money and property and, in some areas, determine the line of family descent. Assignment of intersex babies to the female gender in this community is relatively easy. Nonetheless, the same family anxieties exist which, combined with poor compliance with medication, leads to a good deal of gender change later in childhood. Such a change is sanctioned by law. Amongst the Indian and Chinese families, women are a considerable financial burden and society revolves around the male members of the community. Assignment of an intersex baby as female is very difficult [1]. Similarly, in India, society is said to be happier to accept an inadequate male rather than an inadequate female [2].

Anecdotally, in the Western world most babies were raised as female because the genitalia were easier to reconstruct. This suggests that in many cultures the babies' best medical interests are not the foremost consideration. Although there is no proof that these protocols were true, clinical experience suggests that cultural factors are very influential. This may be no bad thing as there is no 'right' medical answer and the child will have to grow up in the community into which it is born.

Little has been written on the late outcomes of such babies. That which is available mainly concerns easily measurable features such as pregnancy rates. However, future babies should benefit greatly from the broader approach based on quality of life (QoL).

While health-related QoL research in adults has progressed over the past few years, research in children is scanty. In a recent review >30 000 articles on QoL between 1980 and 1998 were identified. Only 12% were related to children, although the proportion has risen in the last 5 years, especially in relation to older children and adolescents [3].

Children with obvious physical deformities have a remarkable ability to adapt. Nonetheless, measurable QoL is adversely affected by the deformity especially if it is exposed to the public gaze, as in changing for sports.

There seems to be a difference between visible abnormalities (such as the absence of a limb) and hidden disorders such as genital anomalies. There is a better emotional outcome with the visible anomalies, especially with interpersonal relationships and self image [4].

A further problem is the limited knowledge about sexuality. Men and animals have been extensively studied but the scientific study of female sexuality is a comparatively new field, at least as far as the surgeon is concerned. Well known researchers such as Kinsey or Masters and Johnson recorded female sexual behaviour and normal sexual physiology. It is only in the 1990s that there has been detailed work on female sexual dysfunction [5]. Some follow-up on vaginoplasty has been limited to assessments of patency, penetration and fertility without considering the quality of the sexual experience. Papers refer to the vagina being 'satisfactory' without saying to whom it was satisfactory or by what means satisfaction was measured.

Such limited assessment may not be totally invalid. The strictly surgical results could be thought of purely in terms of the ability to create a 'vagina' where none previously existed on the presumption that an infant was to be raised as female. However, while it may be self-evident that a penis made from a forearm flap does not have physiological sexual function, the medical establishment may be less aware that a vagina made from intestine is also sexually inert. That a surgeon can make a 'vagina' more easily than a 'penis' should not be a reason, alone, to make a female gender assignment.

It is becoming clear from animal work and from clinical observation that the brain is the most dominant organ in sexual orientation [6,7]. It is therefore not surprising that babies exposed to androgens *in utero* should show some behaviour more often associated with boys, regardless of the appearance of the genitalia. This may particularly be seen in women with congenital adrenal hyperplasia (CAH).

A very interesting group in this respect is women with complete androgen insensitivity syndrome. In this condition the genotype is 46XY and testes are present. There is an androgen receptor gene defect. Although circulating androgen levels are high, no virilization occurs as the tissues cannot respond to androgens. A very detailed investigation of 14 such women showed that they are essentially normal females in their behaviour [8]. This finding obviously weakens the case for the supremacy of the androgen influence on the brain, unless the brain too lacks androgen receptors.

The current revolution, led in part by adult patients themselves, questions previously held notions, requires a flexible approach to allow a change in gender in later life and draws attention to the larger number of affected adults than was previously known. In one of the very few studies of sexuality in adults (eight females and two males), eight thought of themselves as intersexual, although all but one had sexual partners of their own apparent gender [9].

There are examples of patients making more than one change. One child appeared to develop as a male, lived as a female from 4 years old until puberty and then changed back to the male gender [10].

Despite the difficulties in assessing QoL and the success of management in a broader context than 'surgical' outcome, changes in management are demanded; it remains to be seen whether these changes will be for the better.

CAH

Urogenital sinus anomalies are most often associated with CAH; 90% of cases are caused by 21-hydroxylase deficiency and of these, a half to two-thirds will have salt loss as a result of reduced aldosterone production. The anus and rectum are normal. The anatomy of the common path of the vagina and urethra ranges from a complete male type of urethra with a high union of the vagina, to a confluence close to a perineal introitus. The urethral sphincters are likely to be normal.

Almost all cases are identified at birth or occasionally *in utero*. Infants with CAH who have a 46XX genotype will be raised as female. The external genitalia are ambiguous, with an enlarged clitoris which is not corrected with even the most meticulous endocrine control after birth. Surgery in infancy is aimed at separating the two tracts. Recent controversy about the sexual outcome in intersex patients has cast doubt about the extent to which the genitalia should be altered in infancy.

As the urogenital sinus is an obvious anomaly and there is no true vagina, corrective surgery in infancy has long been a standard procedure. The objective is to create separate channels for the urethra and the vagina, and to make the phallus more clitoral in appearance, i.e. feminizing genitoplasty. Surgery to reduce the size of the clitoris has become less radical with time. The results of single-stage feminizing genitoplasty in infants have been widely reported [11,12]. They are better in those with a low confluence of the vagina and urethra.

The timing of vaginal reconstruction appears to have been a matter of contention for at least 25 years. It would seem that only a minority of children are reconstructed in a single operation in infancy or early childhood [13]. In assessing the long-term follow-up of 16 women (of an original 32 children), Lattimer's group concluded in 1976 that the results of vaginoplasty were so poor that the operation should not be done before puberty [14].

TABLE 1 The table shows the number of women born with CAH who have a patent vagina after primary surgery (1ry patency) and the additional number patent after revision surgery (2ry patency). In two of the papers it is possible to divide the patients into those with a low confluence (easy) and a high confluence (difficult). In the report by Alizai et al. *[15] the mean age of the patients was 13.1; although all were postpubertal all were thought to be too young for intercourse to be considered. In [17] intercourse was only considered in 15 patients over 15 years old who completed a questionnaire*

Study	Technically	*n*	1ry patency	2ry patency	Intercourse (%)
[13]	All cases	42	5	33	33 (62)
[16]	Easy cases	25	6	13	11 (44)
	Difficult cases	3	0	1	0
[15]	All cases	13	0	2	0
[17]	Easy cases	20	14	6	4 of 9
	Difficult cases	7	4	2	2 of 6

In Table 1 [13,15–17] the results of four series are given; it can be difficult to determine exactly what surgery was done, when and to whom! It would seem that of 85 evaluable patients 50 were having sexual intercourse (59%). When feminizing genitoplasty is done in infancy, additional surgery around puberty is often required; in all of the patients in the series of Alizai *et al.* [15]. With or without additional surgery after puberty, those who are not salt losers are nearly twice as likely to achieve satisfactory intercourse (87% vs 46%) [13]. The pregnancy rate appears to be higher than the intercourse rate; this anomalous statistic is because the pregnancy rate is given as a percentage of those women who are having intercourse.

It is in this relatively common group that the conflict between the various components of gender identity is most easily seen. The chromosomes are female, the genitalia are ambiguous though verging on the male and the brain has been bathed in androgens *in utero*. The endocrine abnormality is identifiable and can be corrected, although at the price of life-long medication. Compliance with the medical regimen is sometimes incomplete. In what gender do the patients see themselves?

In an early observational study it was shown that CAH women grew up as 'tomboys' and had little interest in role rehearsal for marriage and motherhood [18]. Even though some of these women and been treated late and less completely than would currently be the case, the same group made similar, but less strong, findings more than 10 years later [19].

In an effort to separate the effects of the conflicting components, several control groups have been used and, although none is ideal, a consistent pattern has emerged. When compared with juvenile onset diabetics the differences are very small, with similar sex role-play and feelings of self esteem. This suggests that some of the problem may lie in the chronic nature of the endocrine illness and the medical supervision that is required [20].

However, when compared to their sisters or female cousins, it becomes clear that women with CAH are less feminine and less secure in their female role. In growing up, CAH girls show less inclination to play as, or to form friendships with, other girls, sometimes to the extent of cross-dressing. As adults, although having similar marriage rates, they have fewer experiences of 'true love', up to 20% at least fantasise about homosexual relationships and they have intercourse less often. Up to 13% have gender identity disorder and occasional individuals change to a male gender role. The effects are most marked in those with the salt-losing form of CAH [21–23].

The quality of intercourse seems to be less good in women with CAH than in controls. All the evidence shows the great importance of the clitoris in achieving orgasm. After vaginal reconstruction about half of women will be able to achieve orgasm, but almost always with clitoral stimulation [17]. With a natural vagina treated by regular dilatation all women can achieve orgasm, but if the clitoris has been amputated only 71% can do so [24]. This emphasizes the need to preserve the clitoris.

In a questionnaire survey of patients from my hospital we identified 39 women born with ambiguous genitalia and raised as females. About a half had CAH and a quarter had partial androgen insensitivity syndrome. Twenty-eight (72%) had had clitoral reduction at some stage and 11 had had no clitoral surgery (although three had had vaginal surgery). The mean overall sexual function scores (as assessed by a modified sexual function inventory) were worse in those who had had clitoral surgery. The group that had had clitoral surgery was characterized by the absence of any sexual activity (36%), more widespread sexual problems, especially difficulties with sensuality (78%) and anorgasmia (39%). Only three patients have changed from female to male gender. Interestingly, the results were no different in women recruited from patient groups compared with those attending an endocrine clinic [25].

There is some evidence that surgery even to reduce the size of the clitoris in adults impairs sexual sensation. Four women who had experienced normal sexual intercourse before clitoral surgery were assessed [26]; after standard surgery for clitoral reduction, one maintained normal sexual function, two had difficulty in achieving an orgasm and one was anorgasmic.

When considering clitoral reduction in adults, that which the woman wishes to achieve must be established. The probable damage to sexual sensation must be clearly indicated.

FERTILITY

In deciding on a gender of rearing of any infant with ambiguous genitalia, it is most important to consider in which the child may be fertile. Children with CAH with the 46XX genotype may be fertile as women. Those with 21-hydroxylase, 11β-hydroxylase and 3β-hydroxylase deficiency are potentially fertile. However, infrequent ovulation compounded by poor compliance with steroid replacement therapy reduces the likelihood of pregnancy. The ovulation rate per cycle is only ≈40%, with a good correlation between plasma testosterone and 17-hydroxyprogesterone levels [27].

Until the 1980s, although the fertility rate was known to be ≈60%, reports of successful pregnancy in salt-losers were uncommon [28]. In a relatively large and unselected series of 80 women (half being salt losers) 40 were having heterosexual intercourse. Fifteen of 25 with simple virilization had 25 pregnancies, producing 20 normal children. In contrast, only one of 15 salt-losers became pregnant and she had an elective termination [29].

TABLE 2 The pregnancies reported from 1956 to 1997, adapted from [30], updated to 1999 [28,31]

	Simple virilizing	Salt-wasting	Unspecified	Totals
Women	34	10	18	62
Pregnancies	48	15	28	91
Therapeutic abortion	1	4	6	11
Spontaneous abortion	7	1	5	13
Ectopic pregnancy	1			1
Vaginal delivery of normal child	10	4	2	16
Caesarean delivery of normal child	19	6	14	39
Unspecified delivery of normal child	9			9
Vaginal delivery of CAH child	1			1
Still pregnant at publication			1	1

It would seem that better steroid management has improved the prospects for salt-losers. In a more recent series three of five with salt-wasting CAH and two of three with simple virilizing CAH who were sexually active had eight successful pregnancies [27]. The outcome of pregnancies in a review of the literature from 1956 to 1999 is shown in Table 2 [28,30,31].

Circulating androgen levels in women with CAH increase in pregnancy. In some cases it may be necessary to increase steroid medication (e.g. to 15 mg/day of prednisolone). Placental aromatase activity has been shown to be normal. As maternal androgens undergo aromatization to oestrogen in the placenta, a female fetus will be protected and her genitalia will be normal [30].

SCREENING

It is possible to screen pregnant women for a fetus with CAH, but as the condition occurs in 1 in 14 000 live births, it would be difficult to justify universal screening. However, it is caused by a genetic defect (deletion or conversion of *CYP21*) which may occur in families. Therefore, in pregnancies in high-risk mothers the defect can be sought for in amniotic fluid. The index case will usually be a CAH child born to the mother. As the inheritance follows an autosomal recessive pattern, the risk of a further CAH baby is 25%.

Techniques for fetal diagnosis are improving with time but are already highly specific. The problem is that treatment of the mother must begin before a confirmed diagnosis is available. In a suspect pregnancy, treatment with oral dexamethasone should be started when pregnancy is confirmed at about the fourth or fifth week of gestation (20 μg/kg pre-pregnancy maternal weight in two or three divided doses daily).

Chorionic villus sampling (CVS) can be used at ≈6 weeks; in a series of 31 pregnancies a correct result was obtained in 30 and one was equivocal [32]. Fetal karyotype should be available at ≈8 weeks and treatment stopped if the fetus is male. DNA analysis should be available by ≈10 weeks when treatment is stopped for unaffected fetuses.

Amniocentesis may be used at ≈15 weeks; karyotype, DNA analysis of amniotic cells and (in women who are not already on dexamethasone) 17α-hydroxprogesterone can be determined by the 20th week. A correct prenatal diagnosis was made in all of 55 fetuses in 54 pregnancies (including the case that was indeterminate on CVS) in the series of Karaviti *et al.* [32]. CVS is considered to be the ideal as the result is available earlier. However, it is not possible in all obstetric units and in some cases the mother may present too late in pregnancy.

Follow-up has shown that the genitalia of affected and unaffected fetuses, and the growth milestones in childhood, are normal. Even treatment started as late as 13 weeks is effective. This indicates that dexamethasone treatment of the mother allows correct genital development of affected female fetuses and does not damage the genitalia of

others when given unnecessarily early in pregnancy while awaiting a diagnosis [32].

VAGINAL RECONSTRUCTION

The problem of the woman with any diagnosis and an absent or inadequate vagina is unresolved. At a simple level various techniques for reconstruction are available. None has been shown to produce an ideal substitute for the natural organ and it seems unlikely that any would have the same sexual sensation as the natural vagina. Schober [26], in an extensive review, found that the follow-up assessment was usually confined to the observation that penetrative intercourse was possible, with no attempt to measure its quality. There was little critical evaluation of female sexuality.

Although it is correct to evaluate the quality of intercourse and possible to decide which technique is the best, such surgery is only used to enable penetrative intercourse to take place; it might be said that poor intercourse may be better than none at all.

If the vagina is present but narrow, every effort should be made to enlarge it by progressive self-dilatation. In adults with enthusiasm it is possible to lengthen a vagina from 5 mm to 10 cm with a sufficient diameter for intercourse, over several months, with graded acrylic moulds. The advantage of this technique is that the vagina has normal physiological function, including lubrication during intercourse [24].

There is some conflict about the wisdom of routine dilatation of the vagina after genitoplasty in infancy. Krege *et al.* [17] suggested that it should not be routine if only because of the psychological problems that it may cause (although they offered no evidence for this fear). Gearhart and, even more strongly, Bailez *et al.* [16] recommend dilatation to prevent postoperative stenosis. Despite this, all of the patients in [16] required further minor surgery at puberty to allow intercourse.

Unfortunately, the perineal tissues may be so scarred that dilatation is not possible. Occasionally it may be possible to dilate the vagina under anaesthetic sufficiently that the woman can maintain its calibre with regular dilatation or intercourse. When dilatation is possible the outcome for sexual intercourse appears satisfactory in the few cases that have been reported; in one series all three women with CAH were able to have satisfactory intercourse and two became pregnant. In contrast half of patients (none of whom had CAH) who had various forms of reconstruction complained of bleeding with intercourse [24].

In the few girls with normal internal genitalia and no vagina the timing of surgery is critical and it must be before the menarche. If the window of opportunity is missed, menstruation can be suppressed temporarily with LHRH agonists.

A narrow vagina may be augmented with bowel or skin. A piece of ileum equal in length to the existing vagina and with a long enough pedicle to reach the introitus is selected; it is opened on its antimesenteric border, the vagina opened longitudinally either anteriorly or posteriorly, and sutured 'face to face' with the ileum.

Follow-up has been confined to establishing that intercourse takes place with no undue difficulty. Up to 70% of women who had an intestinal vagina formed in infancy report the ability to have intercourse, with a 10% incidence of dyspareunia [33].

Skin augmentation is usually done by a plastic surgeon using skin from the medial aspect of the thigh. The technique was originally described by Sir Archibald McIndoe in 1938. There have been several modifications, but the principle remains the same; a cavity is created in the position of the vagina and lined with meshed split skin on a mould. The initial complication rate is high, as the skin fails to take in ≈65% of patients. Most will require at least one revision procedure and final surgery is best left until after puberty. About 75% of patients are able to have intercourse (and some of the remainder may be unwilling rather than unable). Self-dilatation with a mould is usually needed in periods of sexual inactivity [34].

Various other tissues have been used as free grafts to line a vagina that has been split open longitudinally. Many of the series are small and the results unpredictable [35].

If the vagina is totally absent, as in the Rokitansky–Meyer syndrome, bowel, skin, amnion and other materials have been used to make a replacement. Again, none is completely satisfactory. Ileum may be too narrow, colon too large and both produce copious smelly mucus. There is a general tendency to make intestinal vaginas too long, which compounds the problem.

Skin on a pedicled flap is rather bulky and split skin has a poor take. The vagina is dry and the squamous lining desquamates, again producing a foul discharge. Amnion has shown quite promising results but availability is limited, especially in the era of HIV infection.

The timing of reconstruction is very important. All of the techniques seem to require some dilatation during childhood. Intestinal vaginas require douching to wash out the mucus. Surgery to enlarge the vagina may be needed at puberty. All of this is done to maintain an organ that, it may be hoped, will not be used for 14 years or more. Perhaps the most compelling argument against surgery in infancy is the risk of neoplasia. In her review, Schober [35] identified five cases of squamous cell carcinoma of skin vaginas and four of adenocarcinoma of intestinal vaginas between 1927 and 1994. The cases occurred in women aged 25–30 years and at 8–25 years after reconstruction. This makes them very rare cancers and none of the relatively large series of vaginal reconstruction report any cases. Nonetheless, the risk remains and a good case can be made for deferring elective surgery until a woman can give her own consent.

SURGERY ON THE CLITORIS

A large clitoris is the most obvious sign of virilization in an infant and the most difficult to disguise if she is to be raised as a female. There is therefore great pressure from parents to reduce the clitoral size as soon as possible. The problem is that current research is emphasizing the prominent role of the clitoris in female sexuality. Schober and Ransley [36] asked 50 normal women to score different genital areas from 1 to 5 for intensity of sexual sensation and ease of achieving orgasm. The clitoris and the area immediately above it scored highest for both (clitoris, mean 3.88 for intensity and 3.0 for ease of orgasm; area above, 3.72 and 2.68, respectively). This finding is supported by a survey of normal female college students, none of whom would have wished to have reductive surgery if they had an enlarged clitoris simply because it was too big. Half of

them would have agreed if they were convinced that it represented a health hazard, and a quarter if it would not alter their sexual sensation (quoted by Schober from conference presentations [26] and Kessler *et al.* unpublished).

Unfortunately it would seem that clitoral reduction surgery reduces clitoral sensation. Minto *et al.* [37] showed that women with intersex who have had clitoral reduction surgery have considerably less sexual sensation than those who have not. Five of 18 who had had clitoral reduction were anorgasmic [37]. Crouch *et al.* [38] measured clitoral thermal, vibratory and light-touch sensory thresholds in the clitoris of six women who had undergone reduction and found significantly increased values in all.

It is possible that these poor results are caused by difficulties of operating on small infants, even though the clitoris is large. However, there is some evidence that surgery to reduce the size of the clitoris even in adults impairs sexual sensation.

With this data it is relatively easy to counsel an adult woman who is considering clitoral reduction; the probable damage to sexual sensation must be clearly indicated. For infants and children, advice to the parents is much more difficult; they have the unenviable task of weighing the short-term advantages of a normal-looking clitoris against the long-term disadvantage of reduced or absent clitoral sensation.

PATIENTS RAISED AS MALE

In considering the sexual outcome in intersex patients raised as males it is important to remember that there is no 'right answer'. Even with the most careful counselling and psychological care, 39% of children have been shown to develop one or more general psychological disorders, regardless of the sex of rearing. Psychological intervention from birth reduces but does not abolish the problem [22].

It is often difficult to establish a diagnosis in genetic or gonadal males with ambiguous genitalia because of the wide variation of phenotypes within any group. In true hermaphrodites with an XY karyotype, all will have some form of vagina and 60% will have a rudimentary uterus. About half have at least one descended gonad. In the androgen insensitivity syndromes, 90% will have some form of vagina but no uterus and 64% have at least one descended gonad. Although testosterone response to chorionic gonadotrophins is near normal in androgen insensitivity and much reduced in gonadal dysgenesis, no diagnosis is possible in about half the cases [39].

There has been a lack of enthusiasm to raise babies with ambiguous genitalia as male, in part because of the apparent success in raising them as girls, particularly until ≈6 years old, and partly through their poor success as boys. In a questionnaire survey of 14 patients with complete androgen insensitivity syndrome raised as females, all were satisfied with their gender. Secondary sexual development was considered to be adequate [8].

In the 1960s, Money, amongst others, championed the view that even totally normal boys could be raised as female providing the decision was made early enough and constantly reinforced. His opinion was based almost entirely on the case of a male infant who had a penile amputation during circumcision. He was castrated and raised as a female. The early success of this biological experiment was not sustained. The patient never felt happy in this role and eventually reverted to the male gender, but not before his case had been widely quoted as a basis for early gender re-assignment in potentially male patients with ambiguous genitalia [40].

At a simple level, lessons can be drawn from babies with abnormal but clearly masculine genitalia. Males born with exstrophy have a short penis with a characteristic dorsal chordee on erection. In the classical form, sexual function as a male has been satisfactory and fertility is possible. However, in cloacal exstrophy the penis may be so rudimentary that sexual intercourse as a male may be impossible. The genotype is 46XY and the testes are histologically normal. Until about 20 years ago there were few survivors and decisions about gender of rearing were largely hypothetical. Now that long-term survival is possible the adult consequences are becoming apparent. Even into early adolescence there has been considerable success in raising the male cloacal exstrophy patients as girls. Furthermore, in the few raised as males, the psychological problems have been overwhelming and there have been reports of criminal behaviour. The evidence on the success of female reassignment is conflicting; it seems that they have role-play behaviour that is masculine, but maintain a female gender identity. Whether this reasonably successful dichotomy will be maintained past puberty remains to be seen [41]. It is not surprising therefore that there has been an unwillingness to raise infants with abnormal or ambiguous genitalia as males. However, there is some evidence that men with abnormal genitalia can have a satisfactory sex life as in classical exstrophy.

In the patients with most severe hypospadias there is a considerable overlap with intersex abnormalities, especially androgen insensitivity syndromes. In one series of posterior hypospadias, 13 of 42 men had a major intersex anomaly. All had severe hypospadias (usually perineo-scrotal) and micropenis [42]. Even with hypospadias as severe as this intercourse still occurs. In a series of 19 patients born with ambiguous genitalia, subsequently determined to be caused by perineal hypospadias, it was reported that 12 had had intercourse, but only four had a regular partner. None of the 13 patients had sperm in their ejaculate [43]. Less good results were given in the other series [42], for although 25 of 42 reported satisfactory erections, masturbation and ejaculation, few had sexual intercourse. Nine of 42 were married and three had children, but only six had a stable relationship.

Men with a very small penis can have satisfying sexual intercourse with female partners. In a series of 20 men with a variety of diagnoses, all were heterosexual in orientation, 75% had a regular partner and none wished to have a gender re-assignment [44].

It seems therefore that an abnormal or rudimentary phallus can form the basis for sexual activity in a male role. Nothing is known of the satisfaction of their partners, but it would be unreasonable to base decisions on the gender of rearing of a baby on the opinions of a putative partner some years in the future.

With the increasing evidence that gender identity is strongly influenced by the hormonal environment of the brain *in utero* and that even very complex problems of infertility can be solved by reproductive technology, there must be a re-evaluation of

previously held truths. Individuals must be helped to achieve that which is possible with the structures available. It is a mistake to amputate sexually sensitive organs without a definite medical reason. Furthermore, it is naïve to think that female sexuality is so simple that inadequate male genitalia can be 'cured' by gender reassignment; there is no evidence to show that the outcome of this policy is satisfactory. Indeed, evidence is emerging to suggest that the outcome is poor; many individuals with ambiguous genitalia would prefer to keep that which they have, rather than have parts reconstructed to produce a copy of a specific gender [26].

The question of fertility is also important. If fertility is possible in one gender it should be given considerable weight in the decision. The techniques that have been developed to allow the direct injection of a single sperm into an ovum (intracytoplasmic sperm injection, ICSI) have revolutionized the prognosis of difficult male-factor infertility. Most countries allow the use of sperm retrieved from ejaculate, epididymis or testis. Sperm can be stored for many years and retain their viability for use in ICSI. The use of sperm precursors is more controversial, both because of poor results and for ethical considerations.

Embryos created *in vitro* by ICSI may be implanted fresh or after cryopreservation. The results for pregnancy, miscarriage, delivery and multiple births are the same for fresh or frozen sperm and embryos, and for ejaculated or epididymal sperm. Nearly 80% of women achieve a delivery and ≈20% have multiple births [45]. Even in azoospermic men where the sperm have been collected from the testis, fertilization is achieved in >80% and a pregnancy develops in >40% [46,47].

Despite the theoretical evidence little is known of the consequences of raising intersex babies as male; while intercourse and even fertility are possible this does not define a 'normal' man. Nonetheless, in the absence of a 'right answer' the same criteria should be applied to potentially male as to potentially female babies. It is unacceptable to say that a baby will make an unsatisfactory man and therefore it will be raised female.

The question then arises as to whether a proper penis can be made. The early management of any case of ambiguous genitalia is that of the underlying condition. With endocrine correction there may be some growth of the penis. Once the boy has passed puberty further growth of the penis is unlikely. Furthermore, from the data available it would seem that where early androgen treatment has produced some penile growth, the position on the centile chart is not maintained. In other words, the penis is only capable of one growth spurt in response to androgens and if that is used up in childhood, puberty will have no further stimulating effect [44]. In rat experiments early androgen treatment produces the shortest penis in adults, whereas treatment delayed until puberty or adolescence results in normal adult length [48].

Dihydrotestosterone cream has also been used to stimulate penile growth; both the penis and prostate show rapid growth. In a series of 22 children there was a mean increase in length of 53% in the first month and a further 18% in the second month of treatment. The series included four boys who had failed to respond to testosterone treatment [49]. Late treatment of a 12-year-old and a 17-year-old boy were reported but the responses were poor [50].

Surgical enlargement of the penis is limited by the inability to make erectile tissue. It is possible to gain length by releasing the corpora from the pubic bone, by dividing the suspensory ligament, but at the price of some loss of erectile stability.

If the penis is completely absent, a new penis can be formed from skin flaps using the techniques developed for gender re-assignment. Good technical results have been reported in boys with micropenis using both groin flaps and a microsurgical transfer of a forearm flap [51,52]. The microsurgical technique is claimed to allow return of sensation and even, with time, of erogenous sensation. No attempt was made to insert prostheses for erection and there is no report on the sexual results (if any).

A technique was described to make a phallus from a skin flap, using the technique for female-to-male gender reassignment, and to 'piggy-back' it onto the natural penis. The man then has his own sexual satisfaction from his small natural penis and can penetrate his partner's vagina with the reconstructed part. The results in patients are reported to be good, with very careful selection [53]. In my very limited experience of the procedure, the appearance is odd and I am doubtful if it can be justified except in those with a very rudimentary natural penis.

When the deep parts of the corpora are present and the pendulous part is absent a very successful reconstruction has been reported using a forearm flap and a segment of radius. The new penis was 'plugged' into the open end of the existing penis. The patient has erections with penile lengthening (based on the original part of the penis), intercourse and orgasm (Santanelli and Paolini, personal communication).

As a general rule, a small penis with natural erections should not be sacrificed but should be used as the basis for sexual function. Every effort should be made to help men to have sexual satisfaction and to this end a knowledgeable sexual therapist is invaluable. Surgery on the penis is often poor treatment for problems that lie in the brain. Only if all else fails and the man is very clear of the likely outcomes should surgery be used to create a large but sexually insensate penis.

IMPACT OF ADULT OUTCOMES ON THE FUTURE MANAGEMENT OF INFANTS

The observation that adult outcome of babies born with intersex disorders is not uniformly satisfactory does not, in any way, imply that earlier management was wrong, let alone malevolent. Medical protocols are based on the best evidence available at the time. They are adapted, slowly, as more information becomes available from science and from the patients themselves. It is always difficult to predict the future and particularly so when a 'right answer' is so elusive.

Only recently were children born with intersex informed of their diagnosis. There may be many adults living perfectly fulfilled lives, unaware that they had an intersex condition. In the questionnaire survey of our hospital patients discussed above, the return rate was only 50%. The other 50% may have normal sexual function and might even be better off without the burden of knowing their diagnosis.

In some intersex conditions intercourse may be impossible without surgery. If the outcome of surgery allows intercourse to take place but is unsatisfactory, it might be that it is better than no intercourse at all.

At one end of the spectrum there is the view that babies could be raised in an indeterminate gender until they are old enough to make their own decision. In a limited way, such a policy is followed in Papua New Guinea, where babies with 5α-reductase deficiency are recognized as an intersex group. In most countries, especially where intersex babies are very rare, society may not be sophisticated enough to cope with an indeterminate gender. Indeed, anecdotally, families in whom there has been a re-assignment of the gender of a baby have had difficulty in coping, often having to re-locate to a new neighbourhood.

In some countries male children are economically more valuable than female; in others, the prospects for sexual intercourse are influential. Gender assignment may be governed by factors that impress the parents and doctors but might be rejected by the child when an adult. It would be virtually impossible to escape from the views of the parents and the wider society in deciding on the management of infants. Nonetheless, it would be hoped that the interests of the child could be put above all others. The patient pressure group, the Intersex Society of North America, advocates at the very least withholding genital surgery until the children are old enough to identify their own sexuality. Such a view seems even more correct when the possibilities for fertility are considered.

If developments continue at the present rate one might imagine that infertility will be abolished altogether. It would seem prudent to manage children on the basis that fertility will be possible so that gonadal tissue and the reproductive organs should be preserved. Where there is a conflict between treatment of a major disease and preservation of fertility, the debate will be intense. The recent advances in reproductive technology have altered the balance of the debate such that future fertility has become a critical issue rather than an improbable dream.

In girls with poor development of the uterus or absent Fallopian tubes, the uterus should be preserved. There have even been anecdotal cases of pregnancy running to term outside a uterus [54,55]. In future, a uterus may not be a prerequisite for a pregnancy.

In some cases the initial management might involve the removal of germinal tissue. It is now possible to store this material in case the decision is later reversed. The practicalities are experimental and the ethical aspects are unresolved. In some European countries, but not in the USA, there is government legislation on the issue. In the United Kingdom, the Human Fertility and Embryology Authority (HFEA) controls that which can be stored, but tissue from prepubertal children is excluded. The Royal College of Obstetricians and Gynaecologists has produced useful guidelines primarily aimed at patients with malignancy, but with relevance to other groups [56]. It is emphasized that the ideal conditions for the collection, storage and unfreezing of germinal tissue are not known and all techniques should be considered experimental. Nonetheless, if storage is not undertaken, the present generation of patients will lose any possibility of parenthood. For both sexes, gonadal tissue may be preserved with the consent of the parents (or child if competent), when treatment is to given that will destroy fertility. The guidelines recommend preserving ovarian tissue for appropriately selected girls.

Testicular tissue can be preserved from prepubertal boys but should only be done as part of an approved research project at present. Spermarche is at a mean age of 13.4 years. The HFEA regulations would apply to any gonadal tissue or sperm from an adolescent at Tanner stage 2 or beyond. Parents cannot give consent on behalf of an adolescent. Tissue or semen would have to be stored on licensed premises.

The subsequent use of stored tissue would require further consent, which could only given by the patient as an adult. In the UK the rules of the HFEA would apply. At present, it is not known to what use the tissues could be put and there are considerable ethical dilemmas both in raising expectations which may not be fulfilled and in predicting the outcome of research yet to be done.

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Correspondence: C.R.J. Woodhouse, The Institute of Urology and Nephrology, University College London, 48 Riding House Street, London W1N 8AA, UK.
e-mail: CWoodhouse2@compuserve.com

Abbreviations: **QoL**, quality of life; **CAH**, congenital adrenal hyperplasia; **CVS**, chorionic villus sampling; **ICSI**, intracytoplasmic sperm injection; **HFEA**, Human Fertility and Embryology Authority.