Objective To establish the spectrum of presentation, natural history and gynaecological outcomes in women with Swyer syndrome.

Design Retrospective notes review.

Setting Tertiary referral centre for disorders of sex development.

Population A total of 29 adult women with Swyer syndrome.

Methods Information was collected on age at diagnosis, biometric characteristics, timing of gonadectomy, histology of gonad, bone mineral density, uterine size and fertility.

Main outcome measures Age at diagnosis, risk of gonadal malignancy, bone mineral density, uterine size and fertility.

Results With regard to presentation, 26/29 (90%) women in this series presented with delayed puberty, and the median age at diagnosis was 17.2 years (range 0–55 years). The median age at gonadectomy was 18 years (range 9–33 years). Histology of the gonad was available in 22 women and demonstrated streak gonads with no evidence of malignancy in 12, dysgerminoma in 7 and gonadoblastoma in 3. The youngest patient diagnosed with dysgerminoma was 10 years old. The median height of the women was 1.73 m (range 1.54–1.95 m). Twelve out of the 20 (60%) women had evidence of osteopenia on dual energy X-ray absorptiometry scan. The uterine size and shape was assessed in eight women after completion of induction of puberty, and the uterine cross-section was found to be significantly lower than that in normal controls. Fertility was achieved with ovum donation in three women, all of whom had live births and one subsequently had a second successful pregnancy.

Conclusion Early diagnosis of Swyer syndrome is necessary in view of the risk of dysgerminoma that can develop at an early age. Adequate hormone replacement is required to maintain bone mineral density and may improve the uterine size and shape.

Keywords Dysgerminoma, gonadal dysgenesis, Swyer syndrome.

Introduction

In 1955, Swyer described two cases of sex reversal that differed from the known forms of what was then termed ‘male pseudohermaphroditism’. The two women had a 46XY karyotype and had primary amenorrhoea, tall stature, female external genitalia (although one had an enlarged clitoris) and normal—albeit hypoestrogenised—vagina and cervix.1 The condition named after Swyer was later linked to dysgenetic gonads and is also known as pure gonadal dysgenesis. Ten to 20% of women with the syndrome have a deletion in the DNA-binding region of the SRY gene,2 while in the remaining 80–90% of cases, the SRY gene is normal and mutations in other testis determining factors are probably implicated.

Individuals with Swyer syndrome are phenotypically female with unambiguously female genital appearance at birth and normal Mullerian structures. The condition usually first becomes apparent in adolescence with delayed puberty and amenorrhoea due to the fact that the gonads have no hormonal or reproductive potential. A high incidence of gonadoblastoma and germ cell malignancies has been reported, and therefore, the current practice is to proceed to a gonadectomy once the diagnosis is made.3

Management of Swyer syndrome is in line with other causes of ovarian failure and involves induction of puberty with estrogen to develop secondary sexual characteristics and long-term combined replacement therapy with estrogen and progesterone. We hypothesised that women with Swyer syndrome have a particularly severe degree of estrogen deficiency as by definition they are completely devoid of any gonadal steroid production. We therefore set out to document the long-term outcome of this syndrome in adults with particular
reference to the estrogen-sensitive endpoints, bone density and uterine size.

**Patients and methods**

Ethics approval was granted by the joint university and hospital ethics committee.

The study was carried out in a tertiary referral centre for disorders of sex development. Twenty-nine adult women with Swyer syndrome are followed up at regular intervals in a specialised multidisciplinary clinic. We performed a retrospective notes review and collected information on age at diagnosis, biometric characteristics (height, weight and breast development), timing of gonadectomy, histology of gonad, bone mineral density and fertility. The delay between presentation and diagnosis of Swyer syndrome was calculated by comparing the date that the woman first presented to her GP to the time that a formal diagnosis of Swyer syndrome was made. No women included in the study had evidence of virilisation, mosaicism or syndromic features.

Women were divided in two age groups to establish whether there was a difference in care among those who had first presented before and after 1990. Under current recommendations, primary amenorrhoea with delayed puberty should be investigated at the age of 14 years. Bearing this in mind, we assumed that those women older than 30 years would have first presented in the 1980s. Thus, we divided women into two cohorts: those older than 30 years and those younger or equal to 30 years.

In eight women, the uterus was assessed by means of ultrasound scanning. In all cases, this was performed at least 2 years after onset of induction of puberty and well after the woman started to menstruate. The uterine cross-section was calculated by multiplying the uterine length (cm) by the anteroposterior diameter (cm) at the level of the fundus. The results were compared with data from 13 normal controls, obtained from healthy, nulliparous women undergoing intrauterine insemination because of male infertility.

**Results**

The median age at the time of the study was 34 years (range 18–59 years). All women had a confirmed karyotype showing 46XY, and one had an abnormal Y chromosome. Testing of the SRY gene was performed in eight women, and one was found to be SRY negative (12.5%).

Information on the age at diagnosis was available in 26 women, and the median age was 17.2 years (range 0–55 years). Twenty-six out of the 29 women (90%) presented in adolescence because of delayed puberty, two of whom had previously been diagnosed and treated for dysgerminoma; however, at the time, there was no suspicion of an unusual karyotype. In one case, the diagnosis was made at birth because prenatal diagnostic testing indicated a male karyotype, and this was discordant with the external genitalia of the newborn. One was tested and diagnosed at the age of 9 years, after her older adolescent sister was diagnosed. One woman presented in her early 50s seeking advice for menopausal symptoms, and it was then noted that she had had primary amenorrhoea that had never been formally investigated. She was diagnosed as having Swyer syndrome at the age of 55 years. Information on the delay from initial presentation to diagnosis was available in 17 women. The median time was 1.5 years (range 0.16–18 years).

Women were divided into two groups of older or younger than 30 years, depending on their current age, to explore the effect of change in modern practice. In those younger than 30 years (12 women), the median age at diagnosis was 16 years (range 0–29 years) with a delay of 6 months (range 0.17–14 years), whereas in women older than 30 years (17 women), the median age at diagnosis was 23 years (range 13–55 years) with a delay of 7 years (range 0.5–18 years).

In 23 cases, information on the age at induction of puberty was available. The median age of commencing estrogen was 17 years (range 13–32 years). Information on current estrogen treatment was also available in 28 women. Of them, 7 women were using the combined oral contraceptive and the remaining 18 were using a variety of hormone replacement therapy (HRT). One woman is still undergoing induction of puberty and is receiving unopposed ethinylestradiol 10 micrograms. Two women in their 50s had stopped taking HRT but were taking bisphosphonates for prevention of osteoporosis.

The median height was 1.73 m (range 1.54–1.95 m), and the median weight was 70 kg (range 47–155 kg). No significant correlation was found between age at presentation, age at diagnosis and age at induction of puberty or menarche and adult height using Spearman’s correlation coefficient.

Twenty-eight out of the 29 women had undergone bilateral gonadectomy. The median delay between diagnosis and gonadectomy was 1 year (range 0.12–14 years), and the median age at gonadectomy was 18 years (range 9–33 years). One woman was counselled regarding gonadectomy but declined.

The histology report was available in 22 cases. Of those, seven women (32%) were diagnosed with dysgerminoma and three (14%) with gonadoblastoma. The remaining 12 cases (54%) had streak gonads. The median age at diagnosis of dysgerminoma was 17 years and ranged between 10 and 31 years. The women who were diagnosed with a gonadoblastoma were 17, 19 and 27 years old.

Results of dual energy X-ray absorptiometry scan performed within the previous 3 years were available in 20 cases. Twelve women (60%) had osteopenia (T score less than –1.0). The median T score of the hip (–0.47, range –2.1 to –1.7) was...
significantly greater than that for the spine (–1.5, range –2.5 to –1.4; \( P = 0.006 \)). Five women (17%) had documented concerns about deficient breast development and three of these women underwent breast augmentation.

The uterine size and shape was assessed by means of ultrasound in eight women. The median uterine length was 62 mm (range 48–82 mm), and the median cross-sectional area was 15.3 cm\(^2\) (range 9.8–21 cm\(^2\)). The cross-sectional area was significantly smaller than that in controls (23 cm\(^2\), range 16.1–31.7 cm\(^2\); \( P = 0.001 \)) (Figure 1). There were no significant differences in weight or body mass index between the two groups. Controls were significantly shorter than patients (1.66 m, range 1.53–1.73 m; \( P = 0.003 \)) (Table 1). There was no significant correlation between height, age and uterine length or cross-sectional area in either group.

Three women achieved pregnancies following egg donation and one of them had two successful pregnancies. Two of the women had term vaginal deliveries and one had a caesarean section at 36 weeks of gestation because of pre-eclampsia. Two other women were contemplating or awaiting egg donation and two women had adopted a child.

**Discussion**

Since the first description of Swyer syndrome in 1955, a number of cases have been reported, but no large series exist in the literature. The exact incidence of the condition is unknown but can be estimated at 1:80 000 births by the fact that we have half as many cases of Swyer syndrome in our Disorder of Sex Development (DSD) clinic compared with complete androgen insensitivity syndrome, which has an estimated incidence of 1 in 40 000. Our study is a unique opportunity to provide information on long-term outcomes for women with Swyer syndrome as a reference for patients and clinicians caring for them.

This study shows that many women experienced delay in reaching an accurate diagnosis. The diagnosis of Swyer syndrome was often only reached several years after presentation to their GPs. The delay appeared to be longer for those women older than 30 years and who first presented as adolescents 15–20 years ago. This would suggest an improvement in timing of diagnosis of Swyer syndrome among younger women, and this probably reflects increasing scientific knowledge and awareness of disorders of sex development among health professionals.

Early diagnosis is likely to be of crucial importance for a number of reasons: first, the risk of gonadal malignancy, second, the early institution of estrogen therapy for induction of puberty and third, to allow for adequate hormone replacement to improve bone mineral density.

The risk of gonadoblastoma and dysgerminoma in women with Swyer syndrome has been estimated to be between 15 to 35%, and current practice is to perform bilateral gonadectomy as soon as the diagnosis is made.\(^4\) It is thought that gonadoblastomas arise from persisting undifferentiated gonadal tissue within the dysgenetic gonad. This tissue is similar in appearance to that found in the embryonic gonad prior to the expression of SRY gene and contains germ cells scattered in stroma and presertoli—granulosa cells.\(^5\) Gonadoblastoma is a form of neoplasm that almost exclusively develops in dysgenetic gonads, and it can occur at a young age. The youngest case reported in the literature was in a 9-month-old infant with ambiguous genitalia.\(^6\) Gonadoblastomas are benign tumours with no metastatic potential; however, they can be precursors to germ cell malignancies, such as dysgerminomas, which is the most commonly associated malignancy, or teratomas, embryonal carcinomas and endodermal sinus tumours.\(^7,8\) In our study, there were seven cases of dysgerminoma. The youngest patient was 10 years old, and three other women were diagnosed with dysgerminomas as teenagers. In two cases, the diagnosis of dysgerminoma preceded by several years the diagnosis of Swyer syndrome as the women first presented with the malignancy and were only later on investigated for delayed puberty.

Early diagnosis of Swyer syndrome in childhood is only possible if a karyotype is carried out for other reasons, such as for example as part of prenatal diagnosis of aneuploidy or as part of familial screening following the diagnosis of a sibling with the condition. Familial cases of Swyer syndrome have indeed been described,\(^9\) and within our series, there was one pair of sisters.

![Figure 1. Uterine cross sectional area (UXA) in women with Swyer syndrome and normal controls.](image-url)
A characteristic and often differentiating feature of women with Swyer syndrome is their increased adult height. In our series, the median height was 173 cm, and all but one woman were taller than 161 cm, which is the average height for English women. The reason for this difference in height is not well understood, and an effect of the Y chromosome has been postulated. In a comparison of published cases of pure gonadal dysgenesis, it was demonstrated that there was a statistically significant difference of 6.6 cm between those with an XX and those with an XY karyotype. It may also be possible that low levels of sex steroids allow for a delayed epiphyseal closure, but no correlation between age at induction of puberty or menarche and final adult height was demonstrated in our series.

An interesting finding in our study was the fact that uterine size of women with Swyer syndrome was smaller when compared with normal controls. This may illustrate deficiencies in the management of women with delayed puberty and hypogonadism, in terms of timing and method of induction of puberty, or it may be due to inherent factors associated with the condition. Studies on Turner syndrome show that the uterus remains small despite estrogen administration. However, women with XX/XO mosaics fair better than those who have a 45XO karyotype, suggesting that factors other than estrogen administration affect uterine development. However, women with a 46XX karyotype who suffer with hypogonadotropic hypogonadism have also been shown to have a smaller uterus when compared with normal controls despite adequate estrogen replacement. The small uterine size, however, did not appear to have an adverse effect on fertility outcome in Swyer syndrome as we found that pregnancies proceeded normally in three of the women and that vaginal delivery was possible.

### Conclusion

Early diagnosis of Swyer syndrome is crucial in view of the high risk of dysgerminoma that can develop at an early age. Although increased awareness over the past 15 years has probably improved the management of these women, it is important that they continue to be followed up in tertiary centres by multidisciplinary teams that are able to provide the multifaceted care that is required in terms of induction of puberty, prevention of osteopenia and fertility. It is also important for these centres to form larger databases to acquire a better understanding of the condition and improve their management.

### Acknowledgements

This work was undertaken at University College London Hospitals and University College London who received a proportion of funding from the Department of Health’s NIHR (National Institute for Health Research) Biomedical Research Centres funding scheme.

### References

10 McDonough PG. In syndromes of confused gonads, height can be important! Fertil Steril 2003;79:462–3.


