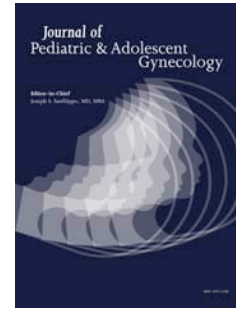


# Accepted Manuscript

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*Incidental gonadal tumours at the time of gonadectomy in women with Swyer syndrome: a case series*

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*Abstract*

*Background:* Swyer syndrome (46XY complete gonadal dysgenesis) is an uncommonly encountered condition in our population. Gonadectomy is recommended upon diagnosis due to a significant risk of malignant transformation of the dysgenetic gonads, typically to dysgerminoma.

*Cases:* We present 3 cases of women who underwent gonadectomy following a diagnosis of Swyer syndrome. Two of these patients had dysgerminoma confirmed on histopathology. In particular we discuss the macroscopic appearance of the affected gonads and the further management of each case.

*Summary and Conclusion:* Individuals with Swyer syndrome require gonadectomy upon diagnosis of their condition, as part of their multidisciplinary management. For treatment of early stage dysgerminoma, surgical resection of the involved gonad and fallopian tube is curative, again highlighting the need for early intervention.

*Introduction*

Swyer syndrome, or 46XY complete gonadal dysgenesis, affects approximately 1 in 30,000-1 in 80,000 women.<sup>1,2</sup> Individuals with Swyer syndrome are phenotypical females, with female genitalia at birth and normal Müllerian structures. These women usually present during adolescence with delayed puberty and primary amenorrhoea, often accompanied by tall stature. The psychosocial and reproductive implications of the condition require multidisciplinary management involving pubertal induction, psychosocial support and assisted reproductive technologies; in addition, the dysgenetic, characteristically “streak” gonads have a 30% risk of development of gonadoblastoma with a 50-60% risk of malignant transformation, typically to dysgerminoma.<sup>3,4,5,6</sup> Therefore, prophylactic gonadectomy is recommended upon diagnosis.

The Statewide Paediatric and Adolescent Gynaecology (PAG) Service at the Royal Brisbane and Women’s Hospital (RBWH), Queensland, Australia, has managed four women with a diagnosis of Swyer syndrome since its inception in 2001. Here we report on laparoscopic and pathologic findings of gonadectomy and salpingectomy in three of the four women, whose histology revealed incidental findings of gonadal tumours of varying severity. The report will also discuss their further management and follow-up.

*Case 1*

The patient was first seen in the PAG clinic aged 17 years, 9 months, having been referred by a paediatric endocrinologist after investigation for primary amenorrhoea. On examination, she had Tanner stage 3 breast development, Tanner stage 5 pubic hair, and normal female external genitalia, with a probe passed approximately 5 cm into the vagina. FSH was 88 U/l (1.0-8.0), LH 26 U/l (1.0-12.0), oestradiol <30 pmol/l, and a 46XY karyotype was confirmed on 2 occasions. LDH was increased pre-operatively at 277 U/l (105-230). Pelvic MRI revealed a small uterus with bilateral gonads visualised. She underwent laparoscopic bilateral gonadectomy and salpingectomy; bilateral streak gonads were noted intraoperatively. Histology revealed bilateral foci of gonadoblastoma with no evidence of invasive germ cell tumour. She was commenced on a low-dose combined oral contraceptive pill after advice was sought from haematology regarding a prothrombin gene mutation on thrombophilia screening (prothrombin 20210G>A heterozygosity). The patient became sexually active aged 19 years with no problems, and has been well on follow-up since.

*Case 2*

The patient was initially seen in the PAG clinic aged 15 years, 8 months, having been referred by a paediatric endocrinologist who had investigated her primary amenorrhoea. She had been investigated for abdominal pain approximately 6 months prior to seeing the endocrinologist and had been treated for *Helicobacter pylori* infection. Pelvic ultrasound at that time had revealed a small uterus and ovaries. On

examination, she was 161cm tall and weighed 53kg, with a BMI of 20.5 kg/m<sup>2</sup>. She had Tanner stage 2 breasts and stage 3 pubic hair, with scant axillary hair. The external genitalia had a normal female appearance and a probe was passed approximately 5cm into the vagina. FSH was 58 U/l, LH 23 U/l, oestradiol 53 pmol/l, and karyotype 46XY on 2 occasions. LDH was normal at 194 and was never increased beyond the reference range. Pelvic MRI revealed female genitalia with volumes of the right ovary and uterus at or just below the reference range for pubertal structures; the left ovary was not identified. The patient underwent laparoscopic gonadal biopsy – operation findings included a small, normal uterus; a left streak gonad (Fig. 1); and a right gonad of abnormal appearance with creamy-yellow surface excrescences, which appeared nodular (Fig. 2). The rest of the abdomen and pelvis appeared normal. Histology of the right gonadal biopsy confirmed a dysgerminoma, described macroscopically as granular cream and tan tissue, arising from a gonadoblastoma, with the left ovary containing gonadoblastoma only. She went on to have laparoscopic bilateral gonadectomy and salpingectomy, and staging, performed by gynaecology-oncology 5 days later. Histology confirmed the previous findings, and peritoneal washings were positive for dysgerminoma cells. This gave her a diagnosis of Stage IC gonadal dysgerminoma, and she underwent 3 cycles of BEP (bleomycin, etoposide and cisplatin) chemotherapy with her local medical oncologist. The patient was commenced on the combined oral contraceptive pill after finishing chemotherapy, which induced menses, and became sexually active at age 16 years, 8 months with no problems. She has been well on follow-up by PAG and gynaecology-oncology since.

*Case 3*

The patient was first seen in the PAG clinic aged 15 years, 11 months having been referred by the paediatric endocrinologist who investigated her primary amenorrhoea. She was 174cm tall, and weighed 66.7kg, with a BMI of 22 kg/m<sup>2</sup>. She had Tanner stage 1 breast and pubic hair, and no axillary hair. External genitalia had a normal female appearance and a probe was passed into the vagina its entire length. FSH was 99 U/l, LH 44 U/l, oestradiol <37 pmol/l and karyotype was confirmed as 46XY on two occasions. LDH was 211 pre-op and was never above the reference range. Pelvic USS was unable to demonstrate uterus and ovaries; kidneys were normal. Bone age was performed and was consistent with 11.5 years. A pelvic MRI revealed a very small hypoplastic or rudimentary uterus with a probable short segment of upper vaginal canal, but mid- and lower vaginal canal not confidently identified, and a probable small right ovary with no left ovary identified; the renal tract was normal. The patient underwent laparoscopic bilateral gonadectomy and salpingectomy during which bilateral streak gonads were identified with the left being slightly yellow in appearance and containing a nodule (Figs. 3 and 4). There was a small rudimentary uterus. Histology of the left gonad revealed dysgerminoma, described macroscopically as a small yellow nodule, arising from gonadoblastoma. As the tumour wasn't surgically staged she underwent CT chest, abdomen and pelvis which were normal. Her case was referred the tumour board meeting of the RBWH gynaecology-oncology service and, given the tiny focus of dysgerminoma, a decision was made for long-term surveillance with regular tumour markers and yearly pelvic

MRIs, with no adjuvant treatment currently. Pubertal induction with oestradiol was commenced under the supervision of paediatric endocrinology, with a view to adding progesterone after 12 months of oestrogen replacement, and the patient was well at her recent post-operative follow-up.

### *Summary and Conclusion*

This case series highlights the importance of prophylactic gonadectomy at diagnosis in women with Swyer syndrome. This condition is not commonly encountered in our population, with just four cases managed by our service in 13 years. The complex, multidisciplinary management of this condition includes gonadectomy, recommended at diagnosis due to the substantial risk of malignant transformation. The outcomes for our small population of women with Swyer syndrome are consistent with the stated risk of malignancy in the literature: of four women with the syndrome, three had incidental gonadal tumours at gonadectomy, two of which were malignant.

Dysgerminoma is the most common malignant germ cell tumour arising from dysgenetic gonads, and is described grossly as a yellow-white to grey-pink, often soft and fleshy mass, consistent with the laparoscopic findings presented here.<sup>7</sup> Early stage disease may be successfully treated with surgical resection of the involved gonad and fallopian tube, ideally with staging performed concurrently.<sup>8</sup> The two-stage procedure performed for the patient in Case 2 is not standard management, and simply reflects a lack of experience in managing women with Swyer syndrome at the time, as this patient was the first case managed by our service. Advanced stage disease can similarly be cured using platinum-based chemotherapy, to which as malignant germ

cell tumours are highly sensitive.<sup>8</sup> This again reinforces the current recommendation for gonadectomy at diagnosis in the setting of 46XY gonadal dysgenesis, as diagnosing any germ cell tumour early in its course allows for a less aggressive treatment approach.

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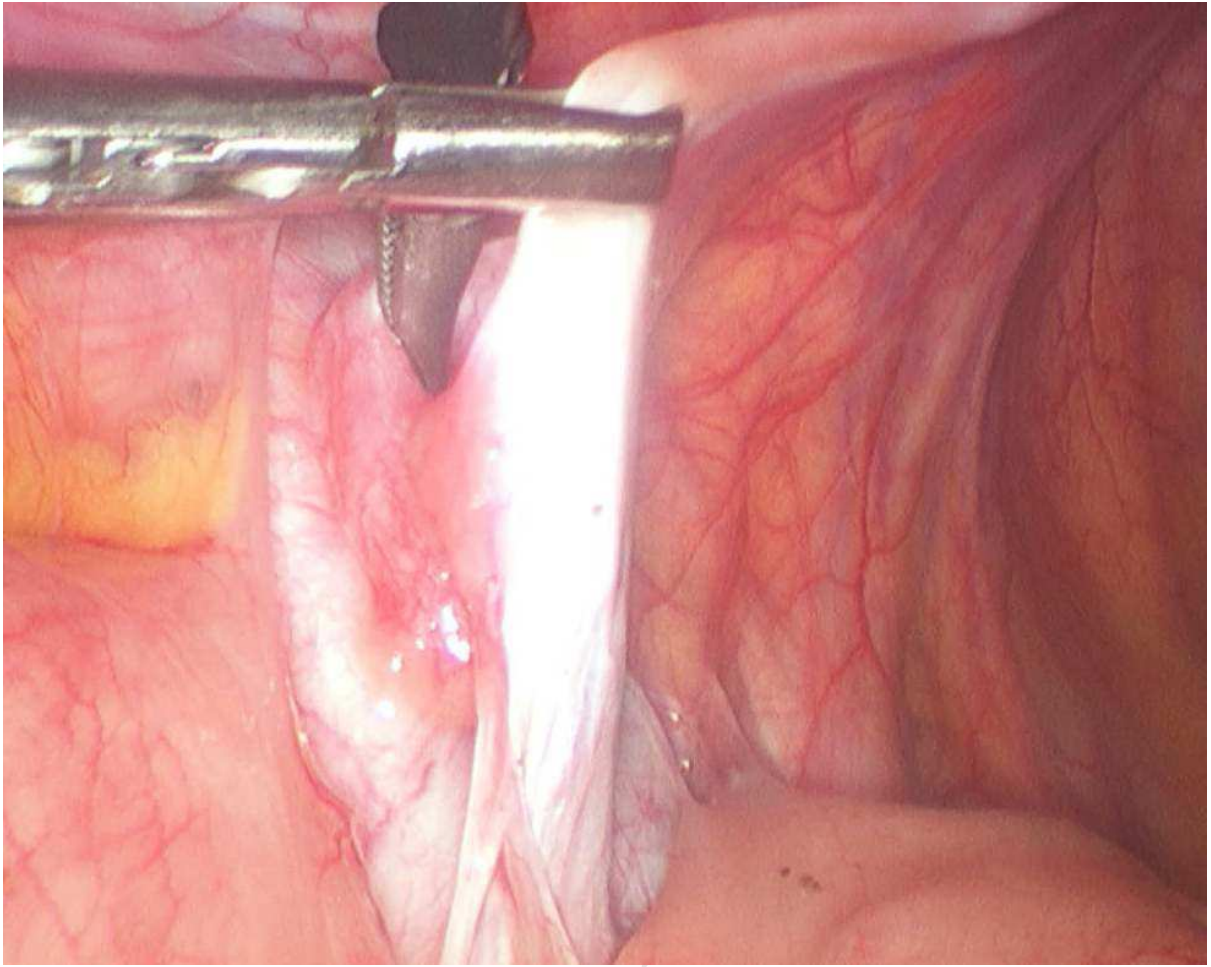
*Figure Legends*

Figure 1. Left streak gonad (grasped) containing gonadoblastoma, Case 2

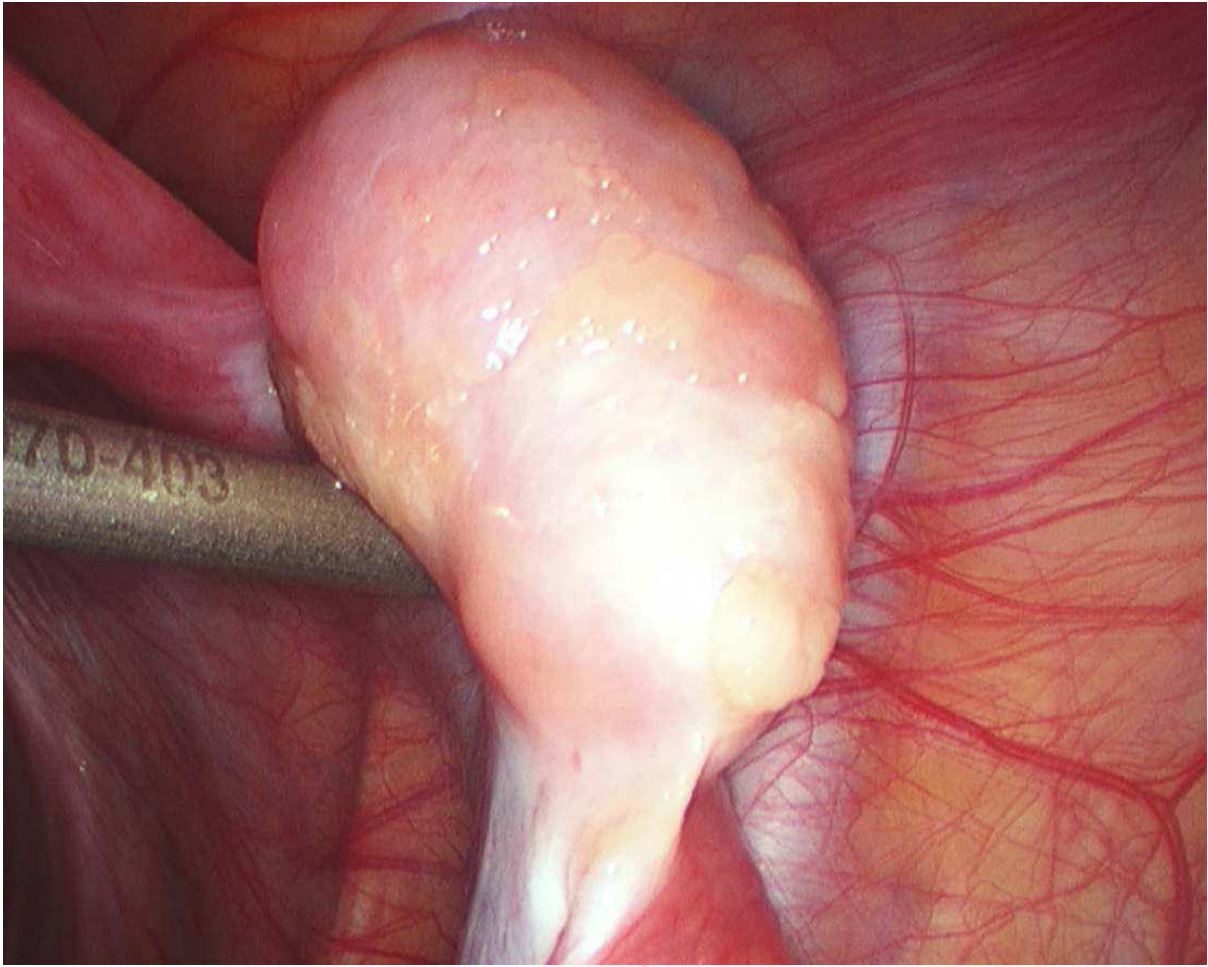
Figure 2. Right gonad containing dysgerminoma arising from gonadoblastoma, Case 2

Figure 3. Right streak gonad, no tumour present, Case 3

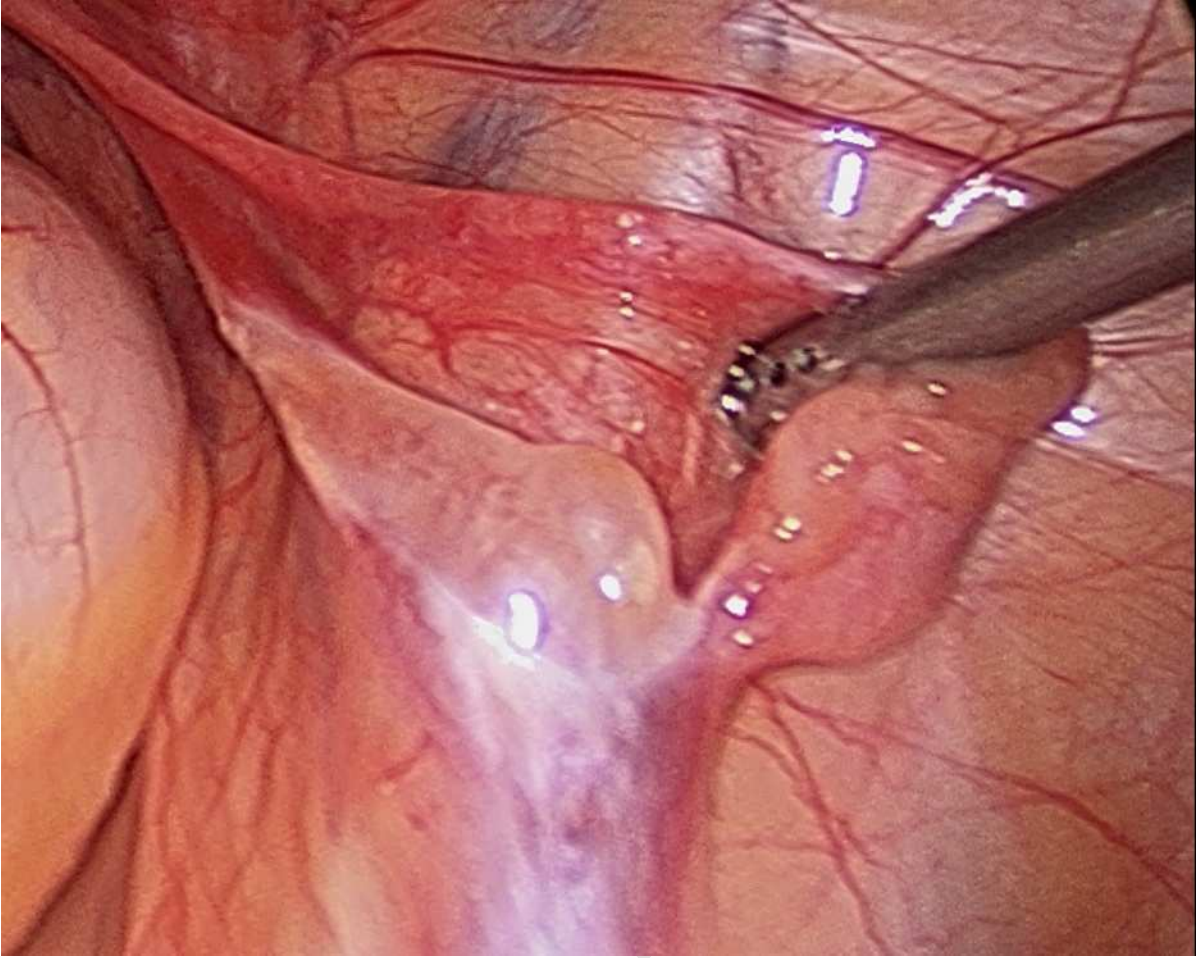
Figure 4. Left streak gonad containing dysgerminoma arising from gonadoblastoma, Case 3



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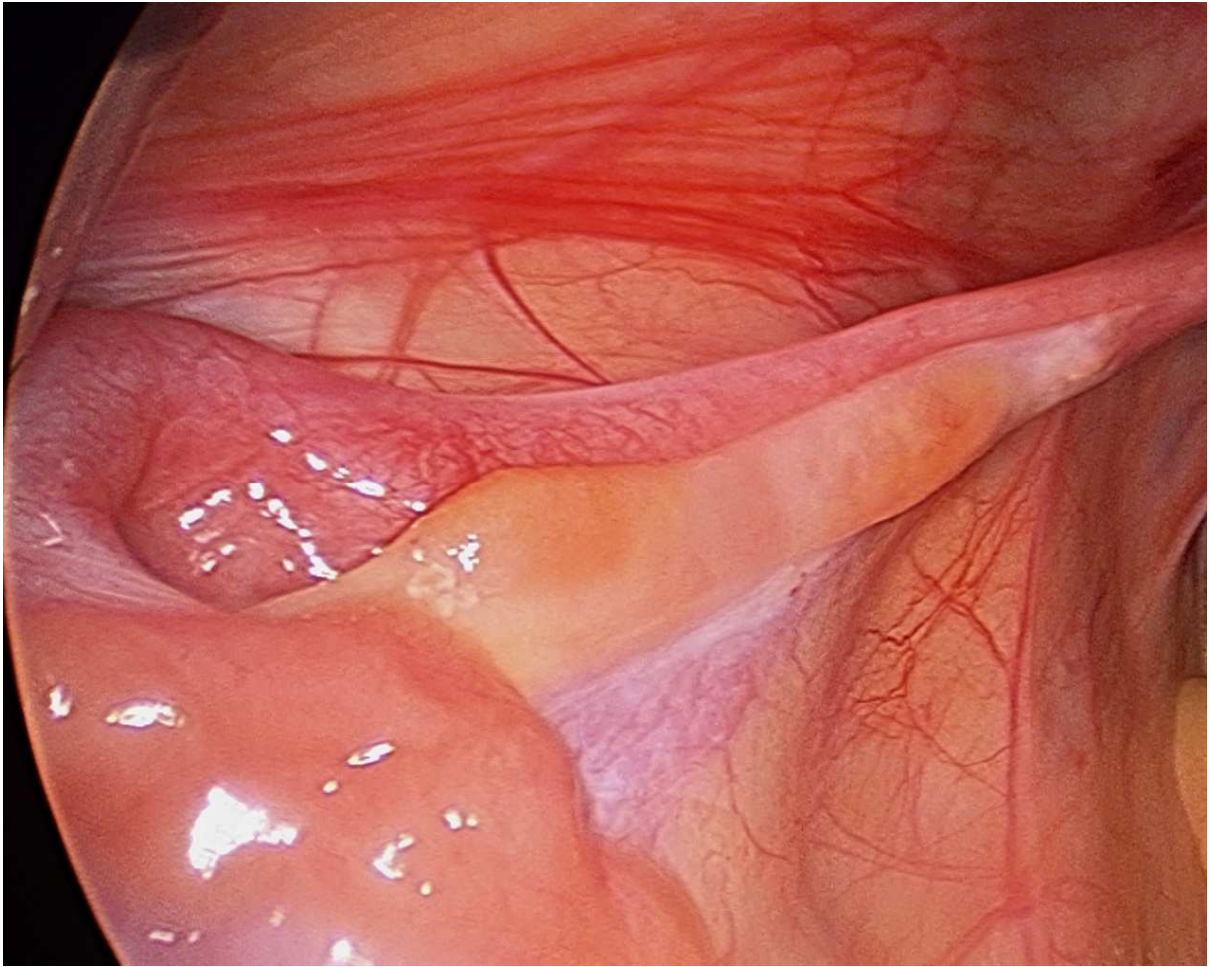


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