PRIMARY OVARIAN INSUFFICIENCY IN ADOLESCENTS: CLINICAL PRESENTATIONS, AETIOLOGY AND INITIAL INVESTIGATIONS

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Introduction

Primary Ovarian Insufficiency (POI) in the adolescent population is uncommon with an estimated incidence of 1:10,000 for women under 20 years of age (ESHRE). It is unclear whether the aetiology of the POI in the adolescent population is similar to adult women. The aim of this study is to characterise the aetiology, clinical presentation and investigations completed in adolescents diagnosed with POI, who presented to the Queensland Statewide Paediatric and Adolescent Gynaecology Service between June 2007 & December 2020.

Methods

A retrospective review was performed of 30 adolescents diagnosed with POI who presented to the Queensland Statewide Paediatric and Adolescent Gynaecology Service, Brisbane, Australia. Cases were identified through the service's database, searching for common POI terms, and then by examining each patient coded as presenting with primary, secondary or oligomenorrhoea. POI cases were included that had an elevated FSH level >25 IU/L, and amenorrhoea for >4 months (1).

Primary outcomes measured was the aetiology of POI. Secondary outcomes included a subgroup analysis of the presentation and investigation of those without chromosome abnormalities (Turner syndrome and those patients with Disorders of Sexual Development (DSD).

Results

The mean age of diagnosis POI of any aetiology was 15.5 years, with an average age of 16.2 years for those with non-chromosome related POI. Most common aetiology were DSD (53%) and Turner Syndrome (20%). Of the remaining 8 cases, 4 were idiopathic POI, 2 ovarian dysgenesis, 1 autoimmune POI and 1 POI secondary to childhood cytotoxic exposure, this case had insufficient data so was excluded from the subgroup analysis. Primary amenorrhoea was the most common presentation (73%).

In the subgroup analysis, 60% presented with secondary amenorrhoea (range 6-12+ months of amenorrhoea) and 40% with primary amenorrhoea. The average breast Tanner stage for those with primary amenorrhoea was 2, whist the secondary amenorrhoea had Tanner stage 4.

Investigations included hormone profile, DHEAS, 17-OHP, prolactin, karyotype and Pelvic ultrasound. In the subgroup analysis, further investigations included repeat hormone profile (71%), anti-Mullerian hormone (AMH) (85%), adrenal antibodies (71%), ovarian antibodies (43%), thyroid peroxidase antibodies (57%), Inhibin B (14%), and investigation for Fragile X (57%). Only 43% (3) patients in the subgroup analysis underwent complete investigation as recommended by peak professional bodies. (1) See Table 1 for incidence of each aspect of POI investigation.

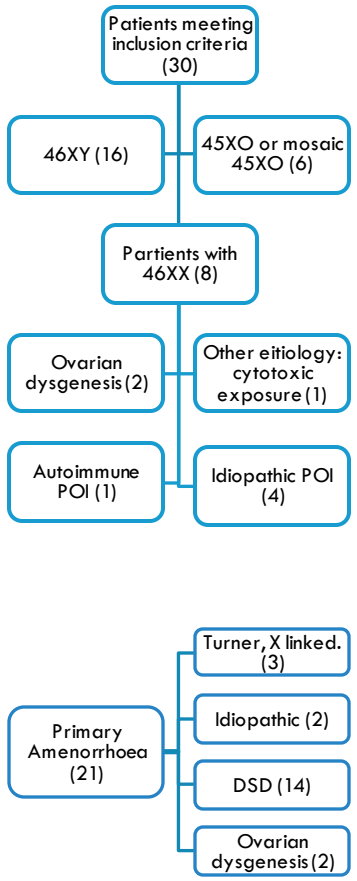

Table 1: Investigations

Variable	n, (%)	Mean ± SD
Laboratory Findings		
Initial FSH	7 (100)	97.6 ± 42.7
Second FSH	5 (71)	
Karyotype	6 (85)	
FMR 1	4 (57)	
AMH	6 (85)	100% <1.0
Inhibin B	1 (14)	<10
17-OHP	7 (100)	100 % normal
Adrenal ab	5 (71)	100% negative
Ovarian ab	3 (43)	100% negative
Thyroid peroxidase ab	4 (57)	1 positive in known thyroid disease
Imaging		
Pelvic US	7 (100)	100% small uterus
Pelvic MRI	3 (43)	
Bone age	3 (43)	All delayed
DEXA	5 (71)	Lumbar Z-score: -1.7 ± 0.1
Complete Investigation?	3 (43)	

References

1. European Society of Human Reproduction and Embryology. Management of women with premature ovarian insufficiency. 2015.

2. Kanner L, Hakim J, Kankanahmge C, Patel V, Yu V, Podany E, et al. Noncytotoxic-related primary ovarian insufficiency in adolescents: Multicenter case series and review. J Paed Adol Gynae. 2018 Dec;31(6):597-604.

Discussion

The most common aetiology for POI in this study were related to DSD and X-chromosome abnormalities, which is consistent with similar studies (2). In adult populations, Fragile X mutations and autoimmunity are common aetiologies for POI in adults (2), whereas in the adolescent population these appear to be of low prevalence, however incomplete investigation may impact these findings.

Oligo/amenorrhoea can be a normal presentation in first 3-5 years post menarche whilst the Hypothalamic- Pituitary- Ovarian axis is still undergoing maturation, however amenorrhoea that is longer than 90 days is on the 10% for cycle length, even within the first year of menarche. The European Society of Human Reproduction and Embryology (ESHRE) recommends a diagnostic criteria of oligo/amenorrhoea for >4 months and two occasions of elevated FSH levels that are >4 weeks apart. (1) In our population, only 71% of the subset population had a diagnostic second FSH completed.

Investigation into POI was variable in our cohort, with 43% having full workup completed. This variability in investigation may lead to delayed diagnosis and treatment, potentially having a lifelong impact. Adolescents with POI are at an increased risk for osteopenia, this risk can be mnimised with timely oestrogen replacement therapy. (2) Although not a part of initial POI investigations, measurement of baseline Bone Mineral Density (BMD) at diagnosis is an important step.

AMH and Inhibin B, although not diagnostic markers for POI, was investigated in 85% and14% respectively. AMH provides a marker of the residual follicle pool, whilst Inhibin B is a predictive factor (alongside oestrogen levels and ovarian follicles seen on ultrasound) in the potential for subsequent ovarian function. (1) These markers are useful for counselling patients and their family about fertility preservation and options.

The recognition of POI in adolescents not only enables timely gynaecology and endocrine input but also facilitates access to reproductive care and appropriate psychological counselling.