Peer Review File

Article information: https://dx.doi.org/10.21037/pm-22-9

Reviewer A

Comment 1. ABSTRACT L.29 "more severe manif" should be changed " more specific Manif" as even limphedema brings TS suspicions.

Reply 1. Appreciate that this more precise and change made.

Comment 2. INTRODUCTION L.95 It is important to highlights that QofL is similar to non-TS women. Abortion should not be recommended.

Reply 2: The results of studies regarding QOL and health related QOL are varied, with some showing compromised QOL and others showing QOL similar to non-TS women. I am reluctant to dive in to QOL in the introduction as it would require lengthy discussion as there is conflict of available literature.

The most recently published studies include:

-Fjermastad showed compromised QOL in 57 adult TS women upon 6 years follow up. (Clin Endocrinol (Oxf) 2016 Sep;85(3):423-9.)

-Reis perfomed systematic review of 559 articles, and showed compromised QOL but unable to determine if height, GH or puberty were related. (Qual Life Res. 2018 Aug;27(8):1985-2006)

-Krantz reported similar HR QoL in adults with TS, some of whom were followed for 20 years. (J Clin Endocrinol Metab. 2019 Nov; 104(11): 5073–5083.)

Comment 3. L.110 A comment about actively looking for Y chromosome material should be done.

Reply 3: A statement about looking for Y sequences in those with virilization was added.

Comment 4. GROWTH FAILURE L.159 . Growth failure " sometimes" not "usually" begins prenatally, and " more often" continues into..

Reply 4: Change in wording made.

Comment 5. OVARIAN FAILURE . It should be commented that not all progestins are the same regarding weight gain in TS.

Reply 5: Added comment about a recent study showing a possible association with weight gain and different progestins.

Comment 6. In the end, L. 293. It is important to discuss with the patients if they want to continue TRH replacement after the " normal" menopause age. There is no study regarding this aspect, though possibilities of decreasing CVD should be noted to the patient. Also, there are studies suggesting their breast cancer risk is lower than in non TS women.

Reply 6: The last paragraph does address this issue with guiding decisions based on patient preference.

Comment 7. CVRisks L.327 Obesity, also a comorbidity commonly found in TS patients Increases the CVD risk.

Reply 7: Added obesity to comorbidities.

Comment 8. NEUROCOGNITION . It should be commented that impaired hearing is very common is TS (50%), and may interfere with their cognitive capabilities.

Reply 8: Agree and added comment about hearing loss and how this may contribute to cognitive processing.

Reviewer B

Comment 1: Other very common aspects of disorder are not detailed.

Reply 1: The focus of this review was in four areas (growth, ovarian failure, cardiovascular disease and neurocognition) so that these issues could be reviewed in detail. Other common

issues were mentioned and included in a table, but were not discussed in depth for this reason. The article could be expanded to include detailed sections on other issues if desired.

Reviewer C

Comment 1. Line 54-64 Introduction could be shortened, this information is already known to the readers.

Reply 1: This paragraph is a basic introduction about TS which seems reasonable to introduce the topic for some readers.

Comment 2. Methods: Please revise this section and add inclusion and exclusion criteria.

Reply: Expanded this section to include inclusion and exclusion criteria.

Comment 3. Diagnostic and Genetics: Authors may consider adding how it has evolved with time. What is the current standard? CVS is a risky procedure, are there any noninvasive cost-effective diagnostics? What's the specificity of these tests and what happens if it is missed on testing? How is this area changed in the last decade or so?

Reply 3: Current standard is noted in the first paragraph which is a standard karyotype.

Section added about non-invasive testing options such as cell free DNA of maternal blood although there is insufficient evidence to recommend currently.

Comment 4. Clinical features: Is anything changed, Is there a consensus on clinical symptoms? What about mosaic TS?

Reply 4: There is discussion about genotype-phenotype associations and mosaicism having milder form, more likely to have spontaneous pregnancies, preserved ovarian function, etc.

Comment 5. I suggest adding a table about the GF, OF, CVD, NC, and SC which provides updates on the last decade and interventions.

Comment 6. I would suggest citing literature from the last 10-12 years to provide an updated review.

Reply: I have included the most recent studies available on each topic, and some of the older studies are included if they are relevant for establishing standards of care.

Comment 7. The author may add a section after the patient is diagnosed with TS, on how to decide about referring to other providers. The author may guide PCP about how and when to involve other specialties.

Reply: A paragraph about multi-disciplinary centers, and networking for families was added. Healthcare checklists and guidelines are available and referenced.