MANAGEMENT OF ENDOCRINE DISEASE

Transition of care for young adult patients with Turner syndrome

Valérie Bernard^{1,2,*}, Bruno Donadille^{1,*}, Tiphaine Le Poulenec^{1,2}, Mariana Nedelcu¹, Laetitia Martinerie^{3,4}, and Sophie Christin-Maitre^{1,2,5}

¹Service d'Endocrinologie et Maladies de la Reproduction, Centre constitutif du centre de Référence des Maladies Endocriniennes Rares de la Croissance et du Développement (CMERCD), Assistance Publique – Hôpitaux de Paris, Hôpital Saint-Antoine, Paris, France, ²Sorbonne Université, F-75012, Paris, France, ³Service d'Endocrinologie Pédiatrique, Centre de Référence des Maladies Endocriniennes Rares de la Croissance et du Développement (CMERCD), Hôpital Robert Debré, Assistance Publique – Hôpitaux de Paris, Paris, France, and ⁴INSERM Unit 1145, Le Kremlin-Bicêtre, Paris, France, and ⁵INSERM UMR_S933, Université Paris Diderot, Sorbonne Paris Cité, Paris, France

*(V Bernard and B Donadille contributed equally to this work)

Correspondence should be addressed to S Christin-Maitre

Email
sophie.christin-maitre@aphp.fr

Abstract

Turner syndrome (TS), affecting 1/2000 to 1/2500 live born girls, is a chromosomal aberration with a total or partial loss of one of the X chromosomes. The diagnosis can be established from the intra-uterine life to adulthood. TS is a chronic disease with particular morbidity and mortality. The loss to follow-up rate, during transition, between children and adult units, remains a crucial issue. This review focusses on the adolescent and young adult patients with TS. The different goals of TS transition are presented as well as some of the tools available in order to improve this transition. The involvement of the patient's family, advocacy groups and therapeutic educational programs are discussed. A specificity concerning TS transition, as compared to other chronic diseases, relies on the fact that patients with TS may present a peculiar neurocognitive profile. They are in general more anxious than the general population. Therefore, psychological support should be offered to optimize transition. Data illustrating the beneficial impact of an organised transition of TS, from paediatric units to multidisciplinary adult care systems, within the same reference centre are presented. Further studies are required to evaluate the mid-to-long-term transition of paediatric patients with TS referred to adult units.

European Journal of Endocrinology
(2019) **180**, R1–R7

Invited Author's profile

Sophie Christin-Maitre MD, PhD, is a Professor of Endocrinology at the Sorbonne University, Paris, France. She works in the UMR_933 research Unit of the National Institute of Medical Research (INSERM), studying genetics of reproductive diseases. She is the Head of the Endocrine Unit, at Saint-Antoine hospital, Assistance Publique – Hôpitaux de Paris. This unit is a member of a Center of Rare Endocrine Disease of Growth and Development (CMERCD). Dr Christin-Maitre's overall research focus is clinical and translational research relating to female and male reproduction. Her interests include primary ovarian insufficiency, Turner syndrome, hormonal replacement therapy and contraception.

Introduction

Transition is defined by the Society for Adolescent Medicine as a 'purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child centred to adult-oriented health care system' (1). Most studies on transition have evaluated immediate transfer from paediatric units to adult units. However, mid-to-long-term transfer in adult health care system of paediatric patients should be assessed.

Turner syndrome (TS), affecting 1/2000 to 1/2500 live born girls, is a chromosomal aberration with total or partial loss of one of the X chromosomes (2, 3). Short stature and primary ovarian insufficiency (POI) are classic features of TS. The prognosis is mainly related to cardiovascular diseases, involving congenital heart diseases, hypertension, aortic dilatation and potential aortic dissection (4).

Recommendations to standardize TS medical care and follow-up have been initially published in 2001, followed by American guidelines and more recently international guidelines (5, 6, 7). The most recent was established following a meeting in Cincinnati, sponsored primarily by the European Society of Endocrinology (ESE) and co-sponsored by the Paediatric Endocrine Society, the European Society of Paediatric Endocrinology (ESPE) and the Endocrine Society (ES) (7).

Different modes of transition of patients with TS from paediatrics to adult units

In the nineties, the group of KR Rubin has proposed several modes of transition for patients with TS (8). The first one is a vertically integrated care model, with paediatric and adult units within the same hospital. It offers the advantage of providing a more simple transition and exchange of health care information from paediatric to adult care by sharing similar physicians, a familiar hospital to the transitioning patient, and the same electronic health records. In the second model, patients have access to paediatric and adult cares within the same health care system but not in a same site of care. The last model involves distinct paediatric and adult care systems. To date, around the world, many patients with TS do not have access to an integrated paediatric-adult multidisciplinary care program.

Studies evaluating TS transition

A lack of appropriate transition for patients with TS has been reported in several studies conducted in Belgium, Australia, France and Poland (9, 10, 11, 12). The largest study included 568 women with TS, with an average age of 22.6 ± 2.6 years (range 18.3–31.2) (11). Only 3.5% of patients with TS underwent all recommended assessments within the 4-year period and 16% had undergone none of the recommended assessments. Multivariate analysis identified the type of physician, as the only factor associated with a better follow-up. This study illustrated the role of endocrinologists, in transition of patients with TS.

What are the key messages to be delivered to patients with TS during transition?

Several visits are usually necessary as many messages need to be delivered to the patient.

The karyotype

A special time should be dedicated to delivering the patient's karyotype. A study from the Turner Syndrome Life Course Project, including 656 women with TS, has recently reported a karyotype–phenotype analysis (13). The authors mentioned that the most common karyotypes are the classical monosomy (45,X: 41.6% of participants) and the 45,X/46,XX mosaicism. Patients with a ring X chromosome (45,X/46,X,r(X): 7.3% of participants) were more likely to have a metabolic syndrome, elevated liver enzymes and higher HbA1C than patients with the classical 45,X karyotype. This study suggested that follow-up of patients with TS could be stratified according to their karyotype. However, according to the international recommendations for the care of patients with TS, information concerning the long term follow-up should be given to all patients with TS, irrespective of their karyotype (7).

Hormonal replacement therapy

As the majority of patients with TS will experience primary ovarian insufficiency (POI) (6, 14), a goal is having patients comply with taking hormonal replacement therapy (HRT), including oestrogens and progestins, up to the age of 50 years (15). The positive benefit-risk ratio of

HRT on skin, bone and heart function should be discussed (16). An important issue is to define with the patient the route of HRT, with oral or transdermal oestrogens (15). Assessing whether the patient wishes or not to have withdrawal bleedings should be taken into account.

Bone density

Measuring bone density can be helpful in convincing patients about the benefits of oestrogens. A recent Australian study has evaluated retrospectively bone density and bone fractures, in an adult population of 76 patients with TS. Despite a median age of 29 years, odds ratio of low bone mass in patients with TS was 9.8 times that of age- and gender-matched controls (17). In this study, the prevalence of non-continuous HRT was high as it reached 40% of the population.

Reproduction

Initially, the physician should take into account the cardiac phenotype and the aortic diameters, as a pregnancy may be contraindicated in some patients with TS with cardiovascular diseases (7). If Y chromosome material is present in the karyotype, bilateral gonadectomy should be discussed in order to reduce the risk of gonadoblastoma (7).

If the patient is still spontaneously menstruating, information should be given that the rate of spontaneous pregnancy is around 6% (18). In such patients, oocyte cryopreservation should be proposed. Indeed, mature oocytes may be obtained after ovarian stimulation. The oocytes are retrieved by transvaginal retrieval and then vitrified for fertility preservation. No pregnancy has been reported, so far, after using cryopreserved oocytes, in patients with TS. When this technique is performed, because of age or non-oncological medical conditions, more than 10–12 oocytes are necessary to obtain a pregnancy (19). Therefore, oocyte cryopreservation does not apply to patients with TS, when their ovarian reserve is too low.

In some cases, ovarian tissue has been preserved during childhood, before the occurrence of POI. No pregnancy has been reported, so far, in patients with TS after using frozen ovarian fragments. Furthermore, the potential impacts of ovarian tissue freezing performed during childhood, on oocyte competence remains quite unknown. Few studies have evaluated such oocyte competence in patients with TS (20, 21, 22, 23, 24). Genetics of 11 oocytes obtained in a young woman with TS (23) have been evaluated by fluorescent *in situ* hybridization analysis.

Among them, none had chromosomal abnormalities. Although this study is rather reassuring, few data are available concerning fertility preservation techniques in patients with TS. A single live birth has been reported, after autograft of ovarian tissue cryopreserved during childhood, in a patient with sickle cell anaemia (25). A single case of live birth after allografting of ovarian cortex between monozygotic twins with TS (45X, 46XX) and discordant ovarian function has been reported (26).

In case of POI, patients should be oriented towards oocyte donation programs. However, repeated careful cardiovascular evaluation is necessary.

Cardiovascular follow-up

During transition, cardiovascular status needs to be re-evaluated (4, 27). The need of a long-term follow-up of aortic dilatation by cardiac magnetic resonance imaging (CMR) and/or transthoracic echocardiography (TTE) has to be explained. The frequency of cardiovascular evaluation is decided according to the initial aortic diameter at the age of 16 years, and the presence of associated cardiovascular risks such as aortic coarctation, hypertension and bicuspid aortic valve. According to the international guidelines, it ranges from every year to 10 years (7).

The main difficulty with TS transition lies in the multiplicity of the necessary exams. Care in adults includes evaluation of liver function, lipid and glucose levels, bone density, audiometric, ophthalmologic and dermatological evaluations as well as autoimmune screening, essentially for thyroid and celiac disease (7). Hearing problems are frequent and are associated with poor quality of life and social isolation. Motivating patients for their lifelong follow-up is a major issue of mid-to-long-term transition.

What are the tools available in order to improve TS transition?

A tool for the transition readiness assessment is provided by The Endocrine Society. It includes 10 questions about health, 16 questions about using health care and 15 questions concerning social and emotional factors. A provider assessment of skill test, a clinical summary and transfer record, as well as a recommended approach for transitioning into adult practice are available on the website (<http://www.endocrinetransitions.org>).

Partners of choice in the field of non-medical actors are advocacy groups (28) (CAIRN.Info). Several of them are involved with TS, such as the Turner Syndrome Support

Society in the UK (tss.org.uk), the Turner Foundation (turnersyndrome.foundation.org) or the Turner Syndrome Society of the United States in the USA (turnersyndrome.org) and AGAT in France (agat-turner.org) or in other countries (please see Orphanet links). Parental and family involvements are crucial for a successful TS transition.

Therapeutic education or personalised care planning may potentially increase the transition's success rate (29). Among endocrine disorders, the most common chronic diseases where transition has been particularly studied are diabetes (30), 21 hydroxylase deficiency (31, 32) or hypopituitarism (33). A Cochrane review on personalised care planning has shown that the effects are not large, but they appear greater when the intervention is more comprehensive, more intensive, and better integrated into routine care (34). Our unit has developed a dedicated therapeutic education program for adult patients with TS. The goal of this program is a pragmatic approach for defining competencies and resources. Each session includes 3–5 patients and lasts 1 day, from 09:00 h to 16:00 h. Patients come from all over France. A nurse trained for therapeutic education performs upon the patient's arrival, an educational diagnosis. Thereafter, a series of four thematic workshops, each lasting 1 h is performed

by physicians from the unit (an endocrinologist, a gynaecologist and a psychiatrist). The workshops deal respectively with feminine, dietary, somatic and psychological issues, related to TS. The discussions during each session are initiated by a homemade educational map (Fig. 1). Each patient shares her own experience with her peers. At the end of the day, patients complete a knowledge assessment on TS. Then, the nurse establishes future targets in order to improve the acceptance of the disease and educative competencies (Supplementary Table 1, see section on [supplementary data](#) given at the end of this article). We are planning to include expert patients, during those sessions.

Specificity of the transition of patients with TS

A major issue in organising TS transition is to take into account the psychology of those patients. Adolescence has been thought to be a high-risk period for girls with TS given their delay in pubertal and linear growth. Furthermore, TS is associated with a peculiar neurocognitive profile. In general, patients suffer from an

Figure 1

Educational map. During the therapeutic education program, each patient with TS shares her own experience with her peers thanks to a home-made educational map. Feminine, somatic and psychological questions related to TS are discussed.

excessive dissatisfaction with self-image and self-esteem (35, 36). Girls or young women with TS are less socially active than unaffected girls of similar age, in terms of time spent with friends or number of friends. This poor adolescent psychosocial integration is explained by a negative body image (37) and in some cases, poor family acceptance of the diagnosis (38). Furthermore, attention deficit hyperactivity disorders (ADHD) are more frequent in TS. A recent study has reported an increased rate of 24% of ADHD in patients with TS, as compared to 1.3% in the general population (39). Therefore, some patients may have specific intellectual difficulties such as organizational, planning or task prioritization disorders (40). A psychological support is important to enhance the patient's self-esteem and to reach a satisfactory quality of life level thus optimizing transition (41).

On the other hand, inflexibility and preoccupation with keeping things in order are often reported in patients with TS (36). Those characteristics should be an advantage, as they should improve compliance for the mid- and long-term follow-up, when immediate transition has been successful.

Results of TS transition in our centre

In order to illustrate this review, we evaluated TS transition in adult patients, followed in our unit, in Saint-Antoine Hospital, Paris, France (Fig. 2). Our unit belongs to a centre of rare diseases, which includes children as well as adults units. It has been labelled by the French Ministry of Health in 2006. It is a member of the European Reference Network on Rare Endocrine conditions (Endo-ERN). Among the 258 patients in our adult unit, 220 (85.3%) have been diagnosed with TS before the age of 20 years. Among those, we distinguished patients who had an 'organised transition', therefore coming directly from paediatric endocrine units ($n=112$) from patients referred by their general practitioner, their gynaecologists or coming spontaneously to our unit ($n=108$). In order to evaluate if the transition had been successful, each patient's electronic file was studied. The frequencies of visits and/or day hospitals were evaluated. Transition was defined as successful if the patient, after an initial visit, came in our unit, at least once, over the past 4 years. This figure was chosen, according to the mean frequency of cardiovascular evaluation, as recommended in the international guidelines (7). As shown in Fig. 2, the mean age at TS diagnosis was similar in both groups.

Figure 2

Evaluation of transition in adult patients with TS followed in Saint-Antoine Hospital (Paris, France). Among the 258 patients in our cohort, 220 (85.3%) have been diagnosed with TS before the age of 20 years. Among those, 112 have transitioned directly from paediatric endocrine units belonging to our reference centre, whereas 108 were addressed indirectly. The number of patients lost to follow-up was statistically lower among the patients referred directly by paediatricians (0/112) vs those who were not (35/108) ($P < 5 \times 10^{-13}$ using a Fisher test).

However, the percentage of patients lost to follow-up was statistically lower among the patients referred directly by paediatricians from our reference centre ($P < 5 \times 10^{-13}$ using a Fisher test). Age at first visit in the adult unit was older in the group without transition, illustrating a lack of follow-up. Although many biases may be present in this evaluation, a paediatric diagnosis followed by a synchronized adult follow-up using a common file was associated with a less frequent loss to follow-up and a higher frequency of visits performed in our adult reference centre. A remaining challenge is to understand why some patients and/or their family have not transferred directly from the paediatric care, where TS was initially diagnosed and followed. A recent review identified the barriers to transition from paediatric to adult care (42). The most common fall within the relationship domains, followed by access/insurance and belief/expectations. Carel *et al.* has shown previously that most socially vulnerable patients may be the one who will be lost at follow-up (11). However, the cost of care should not be involved in the success of transition

in our evaluation, as in France full reimbursement of the patient's care is provided for every patients with TS.

Conclusion

Not so long ago, most young adults with TS were making their way through the healthcare system in an uncoordinated way (1). Hence, inequity of care would affect patients already bearing the burden of a rare disease. A successful health care transition should help other aspects of life, such as work, school or other social issues (1). Young adults with a chronic rare condition like TS need a multidisciplinary approach to their care plan, including psychosocial aspects. Our preliminary data are in favour of an organised transition from paediatric to adult care units, within the same reference centre of rare diseases. Further studies are necessary in order to evaluate failure of transition, essentially the social and/or psychological characteristics of patients with TS.

Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-18-0238>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

References

- Blum RW, Garell D, Hodgman CH, Jorissen TW, Okinow NA, Orr DP & Slap GB. Transition from child-centered to adult health-care systems for adolescents with chronic conditions. A position paper of the Society for Adolescent Medicine. *Journal of Adolescent Health* 1993 **14** 570–576. ([https://doi.org/10.1016/1054-139X\(93\)90143-D](https://doi.org/10.1016/1054-139X(93)90143-D))
- Nielsen J & Wohler M. Chromosome abnormalities found among 34 910 newborn children: results from a 13-year incidence study in Arhus, Denmark. *Human Genetics* 1991 **87** 81–83. (<https://doi.org/10.1007/BF01213097>)
- Stochholm K, Juul S, Juel K, Naeraa RW & Gravholt CH. Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 3897–3902. (<https://doi.org/10.1210/jc.2006-0558>)
- Mortensen KH, Andersen NH & Gravholt CH. Cardiovascular phenotype in Turner syndrome – integrating cardiology, genetics, and endocrinology. *Endocrine Reviews* 2012 **33** 677–714. (<https://doi.org/10.1210/er.2011-1059>)
- Saenger P, Wikland KA, Conway GS, Davenport M, Gravholt CH, Hintz R, Hovatta O, Hultcrantz M, Landin-Wilhelmsen K, Lin A *et al.* Recommendations for the diagnosis and management of Turner syndrome. *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 3061–3069. (<https://doi.org/10.1210/jcem.86.7.7683>)
- Bondy CA. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 10–25. (<https://doi.org/10.1210/jc.2006-1374>)
- Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein KO, Lin AE, Mauras N, Quigley CA, Rubin K *et al.* Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. *European Journal of Endocrinology* 2017 **177** G1–G70. (<https://doi.org/10.1530/EJE-17-0430>)
- Rubin KR. Turner syndrome: transition from pediatrics to adulthood. *Endocrine Practice* 2008 **14** 775–781. (<https://doi.org/10.4158/EP.14.6.775>)
- Verlindé F, Massa G, Lagrou K, Froidecoeur C, Bourguignon JP, Craen M, De Schepper J, Du Caju M, Heinrichs C, François I *et al.* Health and psychosocial status of patients with turner syndrome after transition to adulthood: the Belgian experience. *Hormone Research* 2004 **62** 161–167. (<https://doi.org/10.1159/000080099>)
- Pedreira CC, Hameed R, Kanumakala S & Zacharin M. Health-care problems of Turner syndrome in the adult woman: a cross sectional study of a Victorian cohort and a case for transition. *Internal Medicine Journal* 2006 **36** 54–57. (<https://doi.org/10.1111/j.1445-5994.2005.00990.x>)
- Devernay M, Ecosse E, Coste J & Carel JC. Determinants of medical care for young women with Turner syndrome. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 3408–3413. (<https://doi.org/10.1210/jc.2009-0495>)
- Gawlik A, Kaczor B, Kaminska H, Zachurzok-Buczynska A, Gawlik T & Malecka-Tendera E. Quality of medical follow-up of young women with Turner syndrome treated in one clinical center. *Hormone Research in Paediatrics* 2012 **77** 222–228. (<https://doi.org/10.1159/000337780>)
- Cameron-Pimblett A, La Rosa C, King TFJ, Davies MC & Conway GS. The Turner syndrome life course project: karyotype-phenotype analyses across the lifespan. *Clinical Endocrinology* 2017 **87** 532–538. (<https://doi.org/10.1111/cen.13394>)
- Hreinsson JG, Ojala M, Fridström M, Borgström B, Rasmussen C, Lundqvist M, Tuuri T, Simberg N, Mikkola M, Dunkel L *et al.* Follicles are found in the ovaries of adolescent girls with Turner's syndrome. *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 3618–3623. (<https://doi.org/10.1210/jcem.87.8.8753>)
- Klein KO, Rosenfield R, Santen RJ, Gawlik A, Bäckeljauw P, Gravholt CH, Sas T & Mauras N. Estrogen replacement in turner syndrome: literature review and practical considerations. *Journal of Clinical Endocrinology and Metabolism* 2018 **103** 1790–1803. (<https://doi.org/10.1210/jc.2017-02183>)
- European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI, Webber L, Davies M, Anderson R, Bartlett J, Braat D, Cartwright B, Cifkova R, Muinck Keizer-Schrama S de, Hogervorst E *et al.* ESHRE Guideline: management of women with premature ovarian insufficiency. *Human Reproduction* 2016 **31** 926–937. (<https://doi.org/10.1093/humrep/dew027>)
- Nguyen HH, Wong P, Strauss BJ, Jones G, Ebeling PR, Milat F & Vincent A. Delay in estrogen commencement is associated with lower bone mineral density in Turner syndrome. *Climacteric* 2017 **20** 436–441. (<https://doi.org/10.1080/13697137.2017.1325461>)
- Bernard V, Donadille B, Zenaty D, Courtillot C, Salenave S, Brac de la Perrière A, Albarel F, Fèvre A, Kerlan V, Brue T *et al.* Spontaneous fertility and pregnancy outcomes amongst 480 women with Turner syndrome. *Human Reproduction* 2016 **31** 782–788. (<https://doi.org/10.1093/humrep/dew012>)
- Martinez F & International Society for Fertility Preservation–ESHRE–ASRM Expert Working Group. Update on fertility preservation

- from the Barcelona International Society for Fertility Preservation-ESHRE-ASRM 2015 expert meeting: indications, results and future perspectives. *Fertility and Sterility* 2017 **108** 407–415.e11. (<https://doi.org/10.1016/j.fertnstert.2017.05.024>)
- 20 Kavoussi SK, Fisseha S, Smith YR, Smith GD, Christman GM & Gago LA. Oocyte cryopreservation in a woman with mosaic Turner syndrome: a case report. *Journal of Reproductive Medicine* 2008 **53** 223–226. (<https://europepmc.org/abstract/med/18441731>)
 - 21 El-Shawarby SA, Sharif F, Conway G, Serhal P & Davies M. Oocyte cryopreservation after controlled ovarian hyperstimulation in mosaic Turner syndrome: another fertility preservation option in a dedicated UK clinic. *British Journal of Obstetrics and Gynaecology* 2010 **117** 234–237. (<https://doi.org/10.1111/j.1471-0528.2009.02422.x>)
 - 22 Oktay K, Rodriguez-Wallberg KA & Sahin G. Fertility preservation by ovarian stimulation and oocyte cryopreservation in a 14-year-old adolescent with Turner syndrome mosaicism and impending premature ovarian failure. *Fertility and Sterility* 2010 **94** 753.e15–753.e19. (<https://doi.org/10.1016/j.fertnstert.2010.01.044>)
 - 23 Balen AH, Harris SE, Chambers EL & Picton HM. Conservation of fertility and oocyte genetics in a young woman with mosaic Turner syndrome. *British Journal of Obstetrics and Gynaecology* 2010 **117** 238–242. (<https://doi.org/10.1111/j.1471-0528.2009.02423.x>)
 - 24 Doğer E, Çakıroğlu Y, Ceylan Y, Ulak E, Özdamar Ö & Çalışkan E. Reproductive and obstetric outcomes in mosaic Turner's Syndrome: a cross-sectional study and review of the literature. *Reproductive Biology and Endocrinology* 2015 **13** 59. (<https://doi.org/10.1186/s12958-015-0055-7>)
 - 25 Demeestere I, Simon P, Dedeken L, Moffa F, Tsépélidis S, Brachet C, Delbaere A, Devreker F & Ferster A. Live birth after autograft of ovarian tissue cryopreserved during childhood. *Human Reproduction* 2015 **30** 2107–2109. (<https://doi.org/10.1093/humrep/dev128>)
 - 26 Donnez J, Dolmans MM, Squifflet J, Kerbrat G & Jadoul P. Live birth after allografting of ovarian cortex between monozygotic twins with Turner syndrome (45,XO/46,XX mosaicism) and discordant ovarian function. *Fertility and Sterility* 2011 **96** 1407–1411. (<https://doi.org/10.1016/j.fertnstert.2011.09.012>)
 - 27 Donadille B, Rousseau A, Zenaty D, Cabrol S, Courtillot C, Samara-Boustani D, Salenave S, Monnier-Cholley L, Meuleman C, Jondeau G *et al.* Cardiovascular findings and management in Turner syndrome: insights from a French cohort. *European Journal of Endocrinology* 2012 **167** 517–522. (<https://doi.org/10.1530/EJE-12-0434>)
 - 28 Aymé S, Kole A & Groft S. Empowerment of patients: lessons from the rare diseases community. *Lancet* 2008 **371** 2048–2051. ([https://doi.org/10.1016/S0140-6736\(08\)60875-2](https://doi.org/10.1016/S0140-6736(08)60875-2))
 - 29 WHO. *Therapeutic Patient Education: Continuing Education Programmes for Health Care Providers in the Field of Prevention of Chronic Diseases*. 1998. (https://www.euro.who.int/_data/assets/pdf_file/0007/145294/E63674.pdf)
 - 30 American Diabetes Association. 12. Children and adolescents: standards of medical care in diabetes-2018. *Diabetes Care* 2018 **41** S126–S136. (<https://doi.org/10.2337/dc18-S012>)
 - 31 Speiser PW, Azziz R, Baskin LS, Ghizzoni L, Hensle TW, Merke DP, Meyer-Bahlburg HFL, Miller WL, Montori VM, Oberfield SE *et al.* Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 4133–4160. (<https://doi.org/10.1210/jc.2009-2631>)
 - 32 Bachelot A, Vialon M, Baptiste A, Tejedor I, Elie C, Polak M & Touraine P. Impact of transition on quality of life in patients with congenital adrenal hyperplasia diagnosed during childhood. *Endocrine Connections* 2017 **6** 422–429. (<https://doi.org/10.1530/EC-17-0094>)
 - 33 Ho KKY & 2007 GH Deficiency Consensus Workshop Participants. Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. *European Journal of Endocrinology* 2007 **157** 695–700. (<https://doi.org/10.1530/EJE-07-0631>)
 - 34 Coulter A, Entwistle VA, Eccles A, Ryan S, Shepperd S & Perera R. Personalised care planning for adults with chronic or long-term health conditions. *Cochrane Database of Systematic Reviews* 2015 CD010523. (<https://doi.org/10.1002/14651858.CD010523.pub2>)
 - 35 Amundson E, Boman UW, Barrenäs ML, Bryman I & Landin-Wilhelmsen K. Impact of growth hormone therapy on quality of life in adults with turner syndrome. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 1355–1359. (<https://doi.org/10.1210/jc.2009-1754>)
 - 36 Gawlik A & Malecka-Tendera E. Transitions in endocrinology: treatment of Turner's syndrome during transition. *European Journal of Endocrinology* 2014 **170** R57–R74. (<https://doi.org/10.1530/EJE-13-0900>)
 - 37 Schmidt PJ, Cardoso GMP, Ross JL, Haq N, Rubinow DR & Bondy CA. Shyness, social anxiety, and impaired self-esteem in Turner syndrome and premature ovarian failure. *JAMA* 2006 **295** 1374–1376. (<https://doi.org/10.1001/jama.295.12.1374>)
 - 38 McCauley E, Feuille P, Kushner H & Ross JL. Psychosocial development in adolescents with Turner syndrome. *Journal of Developmental and Behavioral Pediatrics* 2001 **22** 360–365. (<https://doi.org/10.1097/00004703-200112000-00003>)
 - 39 Green T, Naylor PE & Davies W. Attention deficit hyperactivity disorder (ADHD) in phenotypically similar neurogenetic conditions: Turner syndrome and the RASopathies. *Journal of Neurodevelopmental Disorders* 2017 **9** 25. (<https://doi.org/10.1186/s11689-017-9205-x>)
 - 40 Reiss AL, Mazzocco MM, Greenlaw R, Freund LS & Ross JL. Neurodevelopmental effects of X monosomy: a volumetric imaging study. *Annals of Neurology* 1995 **38** 731–738. (<https://doi.org/10.1002/ana.410380507>)
 - 41 Kosteria I & Kanaka-Gantenbein C. Turner Syndrome: transition from childhood to adolescence. *Metabolism: Clinical and Experimental* 2018 **86** 145–153. (<https://doi.org/10.1016/j.metabol.2017.12.016>)
 - 42 Gray WN, Schaefer MR, Resmini-Rawlinson A & Wagoner ST. Barriers to transition from pediatric to adult care: a systematic review. *Journal of Pediatric Psychology* 2017 **43** 488–502. (<https://doi.org/10.1093/jpepsy/jsx142>)

Received 20 March 2018

Revised version received 24 September 2018

Accepted 11 October 2018