

(approx. 4725 words)

Triple-X-syndrome or Trisomy X

Dutch article, published in Patient Care, 2005; 32(6):15-21.

Translated with permission of the journal and slightly adapted.

Translation accomplished with the help of Jill Balfour (KS&A) and agreed with Professor Schrande.

Written by:

Connie T.R.M. Schrande-Stumpel, MD, PhD,
Professor of Clinical Genetics
Academic Hospital Maastricht,
The Netherlands

Maarten Otter, MD,
Psychiatrist

Leopold M.G. Curfs,
Professor of Psychology
Academic Hospital Maastricht
The Netherlands

Address for correspondence:

Connie Schrande-Stumpel, MD, PhD.
Professor of Clinical Genetics
Dept. Of Clinical Genetics
Academic Hospital Maastricht
PO Box 5800
6202 AZ MAASTRICHT
The Netherlands
connie.schrander@gen.unimaas.nl

triple-x-syndrome – chromosome anomaly – prenatal diagnosis

As sex chromosomes men have an X- and an Y-chromosome, women have two X-chromosomes. In approximately 0.1 % of all newborn however a numerical anomaly in the sex chromosomes exists. Boys with an additional X-chromosome have Klinefelter syndrome; girls with only one sex chromosome in most of their cells have Turner syndrome. Turner syndrome and Klinefelter syndrome are examples of sex chromosomal anomalies. Apart from these well known variants there are many other sex-chromosomal anomalies. In this article we focus on the Triple-X-syndrome (trisomy X or 47,XXX-syndrome). There is less knowledge on the Triple-X-syndrome than on the Turner- and Klinefelter syndrome and there is a lack of methodologically well performed scientific research on the various aspects of this condition.

---Express information---

Approximately one out of thousand girls is born with three X-chromosomes. Some of these girls have this 47,XXX-pattern as a mosaic together with a normal 46,XX-pattern. Girls or women with an extra X-chromosome do not always attract medical attention. During pregnancy diagnoses in a fetal girl will only be made when prenatal chromosome analysis is performed. Young girls sometimes show psychomotor and developmental delay; emotional maturation can also be delayed.

From previous studies we know that approximately 1 out of 1000 newborn girls has three X-chromosomes. Some of these girls have the 47,XXX pattern as a mosaic in addition to a normal 46,XX pattern. Dr. Patricia Jacobs and colleagues were the first to describe the so-called Triple-X-syndrome in 1959 in an article in the *Lancet* with the suggestive title 'Evidence for the existence of the human super female'.

Because not every baby undergoes cytogenetic studies, the finding of 47,XXX is per definition a diagnoses in a selected group of girls and women. It is often a coincidental finding, notably after a prenatal diagnosis.

It is also revealed when a chromosome investigation is performed because of a presenting delay in psychomotor development or speech/language delay.

An adult woman with Triple-X is usually diagnosed by coincidence, for example, she may have had a child with a chromosome anomaly or because she had several unexplained miscarriages. Girls and women with an extra X-chromosome usually do not attract medical attention, but when the diagnosis is made, knowledge about the characteristics that possibly can be expected is important. The same holds for the general practitioner.

Clinical presentation

During pregnancy a girl with 47,XXX is diagnosed when, for whatever reason, a prenatal chromosome study is performed. Mostly the maternal age is the indication (see also Case 1). The birth weight is slightly lower, but individually this will not attract medical attention.

No specific external features or specific organ anomalies are reported in this chromosome pattern. They are healthy girls.

Prenatal diagnosis and termination of pregnancies

When Triple-X-syndrome is discovered after prenatal diagnosis, the primary reaction of the parent is often to terminate the pregnancy. Good counselling is essential to give these parents a realistic view of the daughter they are expecting. This counselling is primarily given by the clinical geneticist, often together with a social worker; the general practitioner may have a role in this too. It is also important to contact a parent support group. This gives the parents a chance to be informed about what is known about the syndrome, to give them the best possible opportunity to make an informed decision.

In Denmark between 1970-1984 76% of the prenatally diagnosed fetuses with triple-X were aborted. Between 1985-1987 this figure dropped to 56%. With improved information the number of abortions diminished.

The experience in The Netherlands demonstrates that during the period 1991-2000 33% (18/54) of the couples that were confronted with a prenatal diagnoses 47,XXX elected to abort.¹ If balanced information is provided to prospective parents, pre-natally, the incidence of voluntary termination (abortion) is reduced. Question hereby is if sufficient balanced information is possible based on the present and often quoted literature. Well-substantiated prevalence studies are absent and systematically collected follow-up data are scarce. The same dilemmas also occur at other sexchromosomal anomalies, such as XYY, XXY and XO.

Discussion is important about whether or not performing prenatal examination of the sexchromosomes to avoid above mentioned dilemmas.

Reference:

¹. Nagel HTC, et al. NTVG 2004;148(31):1538-43.

During childhood

When the diagnosis is unknown, nothing or almost nothing will draw attention to the child. They are calm babies and toddlers. However a mild, but significantly slower psychomotor development in comparison with peers is often noticed. Emotional maturation can also be delayed. In comparison to peers a shy and withdrawn behaviour can be seen. A stable home, opportunity to do sports and specific stimulation are all factors that will work positively to contribute to development of the child.

The growth parameters are normal; as for body height the child will be taller compared to peers until about eight years , while the bone age is delayed until ten to twelve years. The legs are relatively long in comparison to peers.

Girls with Triple-X on average have a thicker enamel layer on their teeth than people with a normal karyotype, which might be noticed by a dentist. An increased risk in scoliosis is mentioned in some publications however this can be monitored in annual check-ups (by general practitioner or pediatrician).

The cognitive level in general falls within the lower normal 'range', with IQ averaging in the 80-90 range. When a girl with Triple-X shows a clear mental retardation (MR), further exams are indicated. A mental handicap is more the exception than the rule. In a follow-up study in Denmark none of the girls (n=17) was mentally retarded (IQ below 70). However especially during the first years at school learning problems may appear, reinforcing the need for extra remediation. Learning to read, write and understand mathematics take more time than average. Repetition is very important. Additionally, it is important to maintain the self-confidence in the child. Remedial teaching/Special Education can be much-needed assistance.

---Express information---

Compared to brothers and sisters without a chromosome anomaly, girls with Triple-X-syndrome more often show a delayed speech-/language development. Women with Triple-X-syndrome normally conceive and have children; theoretically there is a slightly increased risk of having a baby with a chromosome anomaly. There is a medical indication for prenatal diagnosis. A normal fetal chromosome pattern generally is found in mothers with Triple-X in the available literature. Possibly, there is an increased risk of psychological and/or psychiatric problems in women with Triple X syndrome.

Speech and language development

In the group of girls with Triple-X-syndrome a delayed speech-/language development occurs more often, certainly in comparison with the brothers and sisters without chromosome anomalies. Speech/Language therapy is important in addition to a hearing examination.

During puberty

Puberty starts at the normal age with the average time of menarche at 12 years. There is no reason to consider hormonal therapy.

At the adult age

For this age group a similar profile applies, so generally there will be fewer 'red flags'. Making social contacts is sometimes described as being difficult. There is discussion about a possible increased risk for psychological and/or psychiatric disorders. Problems have been reported (ie. case 4), but the central question is whether this is a coincidence or whether there is a causal relationship. If these problems occur the psychiatric treatment is the same as for someone without Triple-X-syndrome.

There is limited knowledge about occupation and the type of work chosen, from the scarce and non-representative follow-up data, but it is evident that there are relatively few women that follow academic studies.

Sexual functioning is normal; women with Triple-X are fertile and have children. Prenatal diagnosis is offered because of the possibility of increased risk of having a baby with chromosome anomalies. The available literature so far shows that generally a normal fetal chromosome pattern was found. There is a lack of data to conclude about the age of the menopause.

---Express information---

The extra X-chromosome might be inherited from the mother or the father. However, a non-disjunction in the maternal first meiotic division generally causes Triple-X syndrome. Maternal age is a factor, as in other non-disjunctive situations.

Until now there are no clues for an increased risk for whatever possible condition (or disease). Further scientific data is needed to provide comments on this profile in adult women. Even more than with the questions about the development in the childhood, one must wait for further scientific data to conclude about characteristics of these women at an adult age.

Etiology and pathogenesis as far as known

The extra X-chromosome might come from the father or the mother. However, Triple-X occurs mostly by non-disjunction in the first maternal meiotic division. It is plausible that there is a relationship to the age of the mother. Molecular biological and other pathophysiological aspects have not been the subject of research to date.

Genetic counselling

After the birth of a girl with Triple-X the chance of having another baby with a chromosome anomaly is slightly increased; the woman has a medical indication for invasive prenatal diagnosis (chorionic villus sampling or amniocentesis).

Epilogue

Girls with a Triple-X-syndrome are generally healthy and have (low) normal intelligence. This fact can not be emphasized enough, certainly against the background of the term "syndrome" with Triple-X. However, there are certain areas that might be relevant in individual cases, and (where the girl and her family can merit their benefits). Noting this, the frequent use of the word "can or might" in the above given text is explained.

Many areas of concern, also occur in children without a chromosome anomaly. To avoid unnecessary labelling, caution is recommended in choosing those who must know about the diagnosis. (Even without the possibility of avoiding problems by adequate counseling and treatment of potential pathology). At the moment the risk of a distorted profile of Triple x is present because only specific groups have been studied. For example, children that are diagnosed by prenatal chromosome analyses, or girls/women that are investigated for delayed development or psychiatric problems.

In other words, only those girls who have been diagnosed have been subject to study and they have only been diagnosed because they presented with problems leading to the diagnosis.

It is important to treat the girl as normally as possible and only take the diagnosis (Triple x) into account when problems of a specific nature are observed. For example, if the girl is showing signs of delay in receptive or expressive speech, then the parent will know to seek Speech/Language services. Support of a parent network, or Support Group is recommended, to give thorough and balanced information to parents and caretakers.

Recommended literature:

Parent network: www.triple-x-syndroom.nl

Jacobs PA, Baikie AG, Court Brown WM, MacGregor TN, Maclean N, Harnden DG. 'Evidence for the existence of the human "super female"'. *Lancet*, 1959, 2 423-425.

Nielsen J, Nielsen B.

Most actual info on Danish website: www.aaa.dk/turner/engelsk/triplex.htm.

Pfeiffer RA, Palm D, & Jochmus J. Das Erscheinungsbild der Trisomie des X-Chromosomes bei Jugendlichen (Triple-X-Syndrom) *Monatschrift Kinderheilkunde* 1967; 115(1) 9-18.

Ratcliffe S. Long term outcomes in children of sex chromosomes abnormalities. *Arch Dis Child* 1999; 80; 192-5.

Robinson A, Linden MG, & Bender BG. Prenatal diagnosis of sex chromosome abnormalities in Genetic disorders and the fetus; diagnosis, prevention and treatment. A Milunsky, ed Baltimore London; the John Hopkins Press 1998.

Rovet J, Netley C, Bailey J, Keenan M, Stewart D. Intelligence and achievement in children with extra X aneuploidy; a long term perspective. *Am J Med Genet* 1995; 60; 356-63.

Verp MS, Bombard AT, Simpson JL, Elias S. Parental decision following prenatal diagnosis of fetal chromosome abnormality. *Am J Med Genet* 1988;29;613-22.

Together with Ida Bakker (case 2) Thea van de Velde (case 1) founded the Triple-X parental contact network in The Netherlands and the website www.triple-x-syndroom.nl.

Case 1

Linda was born in 1998 as the third child in the family of Thea and Peter. The oldest child, Patrick, was born in 1995; the second baby Richard died in the end of 1996 after 31 weeks of pregnancy. Thea has a busy life: she is wife and mother, runs the household, works five mornings a week as a telephone operator / receptioniste and takes part in the board of VOGG Philadelphia Eindhoven e.o. (association of parents and relatives of people that are mentally handicapped), where she is the office manager. Peter works as a software engineer at DAF Trucks and also has his own private software developing business.



An amniocentesis was performed for maternal age: in the 19th week the parents heard that they were expecting a daughter with Triple-X-syndrome. That was a big shock! Nobody wants to hear that the expected child is 'different'. Besides that Patrick, their oldest son, is mentally and physically handicapped. And the reason why their son Richard died after 31 weeks of pregnancy is unknown. The first information about Triple-X the parents received from the clinical geneticist was, in addition to an informative conversation, a copy of a 1998 American article. This article did not provide much positive information.

After a search on the Internet Thea and Peter found the article 'Triple-X-females, an orientation' by Johannes Nielsen. This article was more positive. Based on the information available, they decided to continue the pregnancy. Their daughter appeared to have a good chance to have a reasonably normal and happy life (as far as you can predict a thing like that), and the care for Patrick would not suffer too much.

Thea had a normal pregnancy. Labour was induced in the 38th week (because of the death of Richard in the previous pregnancy). She was doing fine right away, weighed about 2.600 grams and was a beautiful baby. Linda developed well. She could walk alone at 15 months and could ride a bike without training wheels when she was 4,5 years. She was potty-trained at 3,5 years in the daytime, at night she was not yet dry until the age of 6,5 years.

Speech development was mildly delayed: she spoke her first words after 2 years of age. They were on the alert for speech delay, but when she went to school (at four years old) she had compensated for her delay and at that time her speech level appeared average. A language test was performed last year which showed that her language understanding and speech level is average.

Thea went back to work when Linda was 4 months. Since then Linda visits a daycare centre 5 mornings a week. She has always liked it very much, but at first she was very quiet for a long time and she did not like it when too many babies came nearby. She still visits the daycare centre on Wednesday afternoons, on days she does not have to go to school and during school holidays.

Linda is presently (2005) in her third year of primary school, without special assistance and finds much pleasure in learning to read and write. Linda's brother Patrick is 2,5 years older and mentally and physically handicapped. He cannot speak, which means that Linda does not have a good role model at home. Linda is very tender with Patrick, but they also regularly quarrel. At the age of 6 years, she is 1.23 meters in height, weighs 26 kilograms and looks perfectly normal. Linda likes to do crafts, jigsaw puzzles, knows what to say and can be an impertinent little girl at times.

Most of the time, Linda does not know how to react to jokes. She can get very angry and upset, and hides herself under a blanket. She cries and carries on relentlessly due to her

misunderstanding. She is pretty insecure over a lot of things. She seems to have problems articulating events that she has recently seen or participated in. For instance she often says she cannot remember what just happened, but her longterm memory is very good.

Sometimes Linda is very shy. When she has to ask something of others (even when she knows them very well), she prefers to leave that to her mother. On the other hand she is rather outgoing, likes to play with other children and sleeps over once in a while, which goes remarkably well. Additionally, she is a bit of a 'tomboy' and likes to wear shorts and pants (only wants to wear a dress to parties). She has more boyfriends than girlfriends, wants her hair cut as short as Patricks, likes to climb trees and climbing frames, loves to be a girlscout etc. Linda loves biking and swimming and almost has her first swimming certificate. Thea and Peter find her to be a wonderful daughter and are really happy to have her in their life!

Case 2

In 1998 Fardau was born after a normal pregnancy and an easy delivery. Her weight was 3.340 kg. Her mother Ida, besides being a mother and a wife, works as a nurse in a hospice (a home for people with terminal diseases) since 2003. Before that she worked in a hospital for 18 years. The father Jan Tjalling is Q.A.-manager in a poultry factory. Before their first child Mark-Jan and in between both full termed pregnancies there was one miscarriage. Because the obstetrician thought she saw a few symptoms of Downs syndrome, Ida and Jan Tjalling decided to have a chromosome examination in Fardau. The results did not show trisomy 21, but by coincidence it was found that she had an extra X chromosome. The pediatrician could not offer them much information, only that it occurred 1:1000 girls and developmental delay could appear. At that time this information did not scare the parents: Ida and Jan Tjalling could see every day that she was a very normal baby.



Genetic counselling brought more reassurance. Fardau could be taller than average, there was a risk for speech and language delay and slight behavioural problems might arise. A supportive and encouraging environment would be of positive influence and therefore very important. Not much reason for a bad faith in her future.

Fardau was a quiet, happy baby and never cried without reason. She had to wear orthopaedic pants for the first 6 months because of a displaced cymbal, but that did not make her less happy. Her motor development was within normal range: she rolled over at six months, she sat alone at 8-9 months, went up on her feet about a month later and she walked unaided at 13,5 months. Since then she is a real climber, wants to stand and hang on everything. The smallest things were picked off the floor which made her parents think there seemed to be nothing wrong with her fine and gross motor-skills. She jabbered a lot, but it took some time before she spoke real words.

As a toddler she had troubles detaching herself. Strangers made her nervous when they started talking to her she would climb up into her mother's arms and cling for comfort. Attending nursery school at 2 years was not very successful. Nine months later she returned and enjoyed it very much. Playing with other children, preferably younger than herself is a favourite thing to do. She has no problems making friends.

Fardau loves babies and toddlers; she likes to mother them. She plays for hours with dolls and baby-carriages, and likes to do handicrafts. Besides that she loves to play outside, riding her bike, tractor and scooter. When she was about 3 years old, she started to put words together but she kept replacing certain letters for others. She knew that she could get a lot of things done by using only sounds and signs, so there was no need for her to try very hard. The doctor at the infant welfare centre did not think her speech development was delayed enough

to recommend speech therapy, as such she was corrected on words she did not pronounce correctly.

Bowel and bladder control took a lot of time and was stressful. What she did not want to do, just did not happen. Three months before she attended school she had bladder control day and night but she was 4,5 years old before she had bowel control. Because she had her bowel movements early in the evening this did not cause any problems at school.

During this entire process Ida and Jan Tjalling learned that Fardau is a girl that does not like to be pushed, but takes her own time to make herself familiar with matters. 'Pushing' her to a proper response simply makes her more resistant. But this may or may not be a normal stage in the development of toddlers. She really loves to go to school. She still has difficulties in group-activities and being the centre of attention, which has to do with being shy and fear of failure, but aren't there a lot of children without a sex chromosome anomaly having the same problems? At school and in other people's homes she is a shy and modest girl but at home she is able to do a lot and can be bossy.

Her emotional expressions, related to the cause, can be somewhat extreme. This means that she screams, kicks and or cries to the extreme. Ignoring this behaviour is the best way to make her stop.

As far as her school performance is concerned there is no indication of any learning problems. Being in the second grade it is remarkable that she still struggles with time terms like yesterday, today, tomorrow, etc. Her short term memory projects a remarkable lack of detail, but her long term memory is extremely sharp. Fardau has a big imagination (fantasy). She uses it to fill in the missing pieces in her stories.

At the age of 5 years and 10 months she is 1.22 meters (her father is 1.94 meters and her mother 1.68) and weighs 24 kilograms.

The above shows that her development has no specific differences compared to a girl without Triple-X. There will be no guaranties, not with any other child, but as far as her development is concerned her parents are not worried at all.

Ida and Jan Tjalling have demonstrated the importance of parent support.

Even though Fardau is too young to understand her condition now, when she grows older she has the right to have sufficient information. What can be better for her then knowing that her parents have done everything in their power to ensure this information for her.

Case 3

Marian is 47 years old and has the Triple-X-syndrome. She did not have any speech-therapy or remedial teaching, but on primary school she repeated a grade once. When she attended secondary school she had an assertiveness training, where she learned to stand up for herself.

She went to domestic science school and after that she followed with training in children- and youth welfare and a training "Care of the mentally handicapped". Afterwards Marian worked for 7 years as a teamleader with mentally handicapped. Nowadays she works in home care. From primary school on she does gymnastics and she sings in a choir for years. Marian does well in groups, but she is not much of a talker. She had her first period when she was 14 and became pregnant approximary 9 months after she stopped taking birth control pills. At the age of 28 Marian found that she had Triple-X-syndrome. Her daughter happened to have the very rare 18p-syndrome. Therefore chromosome examination was indicated in Marian and her husband. They found the Triple-X-syndrome by coincidence! Marians chromosomal anomaly has nothing to do with the 18p-syndrome in her daughter. The doctors told Marian that she might have growth disorders, speech problems and menstruation problems, but she does not have anyone of them. She is not very tall (1.56 meters), but her parents are not tall also. Her



daughter is 18 now and her son Kevin is 15 years old. When Marian was pregnant with Kevin amniocentesis was done, and a normal male chromosome pattern was found. Her periods stopped a year ago. Marian is a normally functioning, healthy woman.

Case 4

Cheryl was born after a normal pregnancy. She's the third child in the family. She developed well and reached all her milestones right on time. She was an active child, which led to a fall from a chest of drawers. Her mother was scared when Cheryl did not react for a while, but a little later Cheryl started to cry uncontrollably. The mother felt guilty about the incident, but Cheryl developed well. Nevertheless her mother insisted on a consultation by a pediatrician. He did not find anything to worry. He saw her for the second and last time when Cheryl was five years old.

During the physical examination he saw a tall (>P90) and skinny (between P25 and P50) girl with a somewhat small head circumference (P25) and signs of a slight delay in the fine motor-skills. An EEG showed a mild aberration with spikes in case of provocation and a somewhat slow activity. A sleep-EEG over 24 hours indicated absence activity, without clinical symptoms.

When Cheryl had difficulties in primary school, her mother wondered if the fall off the chest of drawers might be the cause of this slight delay. Teachers indicated that there was no reason for special education. The other children in the family did not have any problems at school. The eldest children visited a senior general secondary school, higher level.

After primary school Cheryl attended lower vocational training school. She barely managed. She looked somewhat sturdy. Because she reacted rather vehement at home, she was going to live on her own.

Cheryl was admitted a few times to a psychiatric hospital for a crises and diagnosed borderline personality disorder. During her residence, she performed reasonably well for a long period. She provided the staff and nurses with many issues related to suicide and other aberrant behavioural patterns. During the periods she lived on her own, she was often upset, scared and she forced to be admitted for medical help due to her risky behaviour. During periods of crises her medication frequently changed. She has taken several anti-psychotics, mood stabilizers, anti-depressives and benzodiazepines. As a child she responded well to methylfenidate (Ritalin®). This did not produce the desired result: long term stabilization.

During her periods of residence she seemed to react strongly to the atmosphere of the group. If the group was restless, she often chose to be excused. When she was admitted once again, a psychological examination was requested. The result was an IQ compatible with a mild mental retardation. This was not in accordance with former test results.

She was placed with caretakers for mentally handicapped children, but they did not know how to deal with her psychopathology. Finally she was admitted for observation and diagnosis in a setting where both her psychiatric problems and her mental limitations were better understood.

At that moment it became obvious that the traditional methods of handling psychiatric patients was not suitable for Cheryl. A more caring and pedagogical approach without pushing in a certain direction worked better. Explaining and calmly negotiating "next steps", without time pressure, had better results.

The paranoid psychotic symptoms she showed (there are no further signs and symptoms of schizophrenia!), decreased after we introduced clozapine (Leponex® or Clozaril®). Her brainscan showed a picture with somewhat deeper sulci and bigger ventricles. Because of the mild mental retardation chromosome study was performed: a 47,XXX pattern was documented in the majority of the cells.

Comment of the authors:

In daily practice women with Triple-X syndrome are known to have a precarious development. The critical question is whether these findings are coincidental or whether they are related to the Triple-X syndrome.

August 2005, translated from Dutch

Thea and Peter van de Velde

Dutch Parent Support Group Triple-X-syndrome

Langsteek 15

5641 NG Eindhoven

The Netherlands

info@triple-x-syndroom.nl

www.triple-x-syndroom.nl

phone (31) 40 2810261