Turner karyotype and childbirth

by

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Happy family, one month after birth of a lovely daughter. With permission from Madelen and Jimmy. Madelen is one of many women with TS.
Abstract

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Turner syndrome (TS) is a sex chromosome aberration and occurs in 1/2500 live born girls. One X chromosome is absent or structurally changed in all (monosomy) or some (mosaicism) of the cells. TS is characterized by short stature, ovarian failure and cardiac defects. Mortality is increased, mostly owing to cardiovascular disease and aortic dissection. Pregnancies in women with TS are rare, but have increased owing to oocyte donation (OD) and are reported to be of high risk.

The aim of this thesis was to describe characteristics of mothers to girls with TS and characteristics of newborns with TS and to evaluate the obstetric and neonatal outcomes in women with Turner karyotype and whether the pregnancy increased morbidity after delivery.

Characteristics of mothers giving birth to girls with TS from 1973-2006 and their newborns with TS were investigated in a study using the Swedish Genetic Turner Register (SGTR) and the Swedish Medical Register (MBR). Mothers to girls with TS were older and shorter than mothers from the general population. More girls with TS were born late preterm and were small for gestational age than controls. In a registry study, using the SGTR, the MBR, and the Cause of Death Register (CDR), 115 women with Turner karyotype who gave birth to 208 children (after both spontaneous and OD pregnancies) born 1973-2007, were studied. One woman had an aortic dissection. Singleton of women with Turner karyotype had lower gestational age, but similar size at birth and the rate of birth defects did not differ. In a Nordic, descriptive study on women with TS who had delivered after OD 106, women and 131 children born from 1992-2011 were included, and data from medical records were registered. The rate of hypertensive disorders during pregnancy was 35%. Life-threatening events occurred in four pregnancies (3.3%) including one with aortic dissection. The rate of preterm birth was 8% and low birth weight 9%. In a population-based registry study, mortality and morbidity in 124 women with Turner karyotype who had given birth from 1973-2010 was compared with women with Turner karyotype without childbirth and a control group from the MBR. The SGTR, the MBR, the National Patient Register, the CDR and Cancer Register were used. Morbidity and mortality in the total Turner group were increased as compared with the controls. Morbidity from cardiovascular diseases was increased before and during pregnancy but similar after more than one year after delivery and no deaths were seen.

In conclusion, pregnancies in women with TS are high risk pregnancies owing to hypertensive disorders and aortic dissection. Neonatal outcomes in women with TS are generally reassuring. Women who gave birth to girls with TS were shorter and older.

Key words: Turner syndrome, obstetric, neonatal outcome, Turner karyotype, pregnancy, maternal, neonatal characteristics.

Göteborg 2013
Svensk sammanfattning


Syftet var dels att studera karaktäristika hos mödrar till flickor med TS och hos nyfödda flickor med TS, dels det obstetiska och neonatala utfallet samt sjuklighet eller risk för död under graviditet och åren efter förlossning hos kvinnor med TS.


Inget dödsfall inträffade. Andelen barn födda för tidigt var 8% och andelen barn som hade låg födelsevikt var 9% vid singelgraviditet. Tvillinggraviditet medförde högre risker både för mor och barn, jämfört med singelgraviditet.

**Sammanfattningsvis:** Mödrar till flickor med TS var äldre och kortare än mödrar i populationen. Graviditeter hos kvinnor med Turner karyotyp är högriskgraviditeter på grund av risken för hypertensiv sjukdom och aortadissektion. Vid äggdonation är ett-embryo-återinförande en absolut rekommendation. Neonatalt utfall var i allmänhet gott och bättre än vad som tidigare har rapporterats.
This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I. Women who gave birth to girls with Turner syndrome: maternal and neonatal characteristics
*Human Reproduction* 2010; 25(6):1553-1560

II. Obstetric outcomes in women with Turner karyotype
*Journal of Clinical Endocrinology and Metabolism* 2011; 96:3475-3482

III. Obstetric and neonatal outcome after oocyte donation in 106 women with Turner syndrome: a Nordic cohort study
*Human Reproduction* 27 March 2013 PMID:23539610

IV. Morbidity and mortality after childbirth in women with Turner karyotype
*Human Reproduction* 2013, In press

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<tr>
<td>AMH</td>
<td>anti Müllerian Hormone</td>
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<td>AOR</td>
<td>adjusted odds ratio</td>
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<td>ART</td>
<td>assisted reproductive technologies</td>
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<td>ASI</td>
<td>aortic size index</td>
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<td>American Society for Reproductive Medicine</td>
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<td>BAV</td>
<td>bicuspid aortic valve</td>
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<td>body mass index</td>
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<td>CI</td>
<td>confidence interval</td>
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<td>central personal registry</td>
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<td>FSH</td>
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<td>HELLP</td>
<td>haemolysis, elevated liver enzymes, low platelet</td>
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<td>hormone replacement therapy</td>
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<td>ICD</td>
<td>international classification of diseases</td>
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<td>in vitro fertilization</td>
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<td>low birth weight</td>
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<td>NPR</td>
<td>National Patient Registry</td>
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<td>oocyte donation</td>
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<td>odds ratio</td>
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<td>PTB</td>
<td>preterm birth</td>
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<td>SC</td>
<td>spontaneous conception</td>
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<td>SD</td>
<td>standard deviation</td>
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<td>small for gestational age</td>
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<td>SMR</td>
<td>standardized mortality ratio</td>
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<td>Turner syndrome</td>
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<td>vacuum extraction</td>
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<tr>
<td>VLBW</td>
<td>very low birth weight</td>
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<td>VPTB</td>
<td>very preterm birth</td>
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Introduction

History

The science of modern genetics was founded by G. Mendel in the 1860s. Since the late nineteenth century and early twentieth century there have been huge developments in this science. From initially describing simple inherited attributes in parents and children, today complex inherited disorders are described. The characterization of the entire human genome has changed medical science. The possibilities of understanding, diagnosing, treating and curing disorders and diseases are far beyond what anyone could ever have imagined in the early days of this scientific discipline.

In 1933, American geneticist T.H. Morgan was awarded the Nobel Prize in medicine for the discovery that genes were localized in the chromosomes. Technical improvements and the possibility of swelling cells by using hypotonic solutions and studying the ‘unclottered’ chromosomes led to the discovery of the correct number of 46 chromosomes in the human being, by Joe Hin Tjio and Albert Levan, Sweden (1, 2). In 1959, the precise chromosome aberrations, the karyotypes causing Down’s syndrome, Klinefelter’s syndrome and Turner syndrome (TS) were demonstrated (3, 4). The terms genotype and phenotype were coined by W.L. Johannsen, a Danish professor, in the Elemente der exakten Erblichkeitslehre in 1913 (5).

The phenotype of girls and women with a 45,X karyotype was described before the genotype was known. The first description was made in 1925 at a meeting at the Russian Endocrinological Society by N.A. Šereševkij (6), and thereafter by Otto Ullrich and by Henry Turner in 1938 (7). The common features of the girls described were short stature, sexual infantilism and webbed neck. In most countries the syndrome is known as Turner syndrome (TS).

Today the diagnosing of TS is a combination of genotype and phenotype. Most cases of TS have both the typical stigmata and genotype. In some cases a Turner karyotype is diagnosed even when the typical stigmata of TS are lacking.

The diagnosis of TS is important because it opens up the possibility to prevent very short stature, inducting puberty and treat infertility and because of the increased risk of serious morbidity, especially cardiovascular complications.
Phenotype

Clinical features are shown in figure 1. The most common features are short stature and ovarian insufficiency.

Cardiovascular malformations are common and important findings in women with TS. They occur in up to 40%, possibly more (8-11) of all women. The most common cardiac defects are left sided ones with bicuspid aortic valves (BAV) (18-32%), aortic coarctation (2-12%) and aortic root dilation (12-32%). Aortic root dilation is often seen in association with other cardiac abnormalities (11-14) (Figure 2).

Renal and urogenital tract malformations occur in 29-42%. The most common malformations are horse shoe kidneys and a double ureteric system (15, 16).

External stigmata
- Short stature (>85%)
- Low posterior hairline
- Webbed neck
- No breast development
- Increased intermamillary distance, broad chest
- Foot and hand lymphedema
- Eyes
  - Epicanthus fold, ptos, strabismus
- Mouth
  - Arched palate
- Ears
  - Hearing loss, low set ears
- Skin
  - Multiple naevi, keloid
- Skeletal
  - Genu valgus, cubitus valgus, short metacarpal IV, scoliosis TS

Internal stigmata
- Ovarian streaks
- Cardiac defects, often left sided
  - Bicuspid aortic valves
  - Aortic coarctation
  - Aortic dilation
- Kidney defects
  - Renal aplasia
  - Horseshoe kidney
  - Double pelvis/ureters

Figure 1. Most common stigmata in girls and women with TS. From A Hagman.
Genotype

The karyotype is the picture or map of an individual’s genotype or the description of the person’s chromosomal constitution. In individuals with TS the female phenotype and typical genotype is required. Karyotypes include complete absence of the second X-chromosome, or a structural change in one or both of the X-chromosomes or a numerical change in the second X-chromosome, in all or some cells. Monosomy 45,X (Figure 3) is the most common (40-50%) karyotype, followed by mosaicism 45,X/46,XX (20-25%) or multiple X in the second cell line, isochromosome 45,X/46,X i(Xq) or 46,X i(Xq), ring chromosome 45,X/46 X r(X), deletion X 45,X/46,X,del(X) or 46,X,del(X), fragment of Y or other structural abnormalities of the second X-chromosome (20-30%) (17). The grade of mosaicism has been studied by Homer and co-workers (18). They found corresponding TS features in women with mosaicism from 6% 45,X/46,XX. El-Mansoury postulated that chromosomal mosaicism mitigates stigmata and cardiovascular risk factors in TS (19). The majority of TS cases are sporadic. Meiotic non-disjunction is thought to be one of the most important causes of TS and the non-disjunction during mitosis during early embryonal development is an important cause of mosaicism (Figure 4). The normal XX cell line has been describe as being
of maternal origin in about 70%-85% (20, 21). TS is also caused by structural defects of the X chromosome such as deletion of the p- or q-arm (delXp or delXq), isochromosome Xq i(X)(q10) and ring X r(X) (1). In these cases mosaicism is common. Transmission from mothers to daughters is mainly described in these latter karyotypes (22-24). Mosaic TS karyotypes also include 45,X/47,XXX and multiple X can also occur.

Maternal age has not been proven to be of the same dignity in the risk of having a girl with TS as it has in trisomies (25, 26), but both young maternal age and more mature age at childbirth ave been discussed.

**Figure 3.** A monosomy, 45,X karyotype is shown.

**Figure 4.** A meiotic non-disjunction is shown. One normal cell fails to separate and one daughter cell will have two of the chromosomes (disomic) and the other none (nullisomic). This can occur in both meiosis I and II as well as in mitosis.
Introduction

Chromosome analysis

When investigating for a chromosome abnormality the person is in most cases tested by a blood sample, for examining lymphocytes. It is also possible to investigate other tissues such as cells from buccal tissue, ovarian tissue, fibroblasts, amniotic fluid or chorionic villi sample. The karyotype can differ when analyzed in different tissues in the same individual. A woman with 45,X in lymphocytes can be found to have a mosaic karyotype after her ovarian tissue is investigated (27).

At least 30 cells should be counted in order to identify at least 10% mosaicism, according to recommendations from the American College of Medical Genetics (ACMG) (28). This has been the practice in Sweden since 1994. If this does not reveal a mosaicism, but the suspicion is still strong more metaphases should be counted and fluorescence in situ hybridization (FISH) is appropriate to use to detect even low levels of mosaicism.

Prenatal testing

Prenatal screening has been in increasing use for at least two decades. Foetuses with TS, especially monosomy 45,X may have typical features in ultrasonography with cystic hygroma, nuchal thickening, coarctation of aorta and left-sided heart defects. In general, foetuses with mosaicism do not have these features to the same extent and female foetuses without such ultrasonographic results may, when new born have few if any stigmata. The prenatal Turner karyotype based on chorionic villus or amniotic fluid cells cannot exactly predict the phenotype. According to ACMG (28), girls with incidental prenatal findings associated with TS and the absence of ultrasound findings have less severe phenotypes with fewer abnormalities than those diagnosed on the basis of ultrasound findings. Abortions often occur spontaneously in 45,X fetuses, but there are also induced abortions in pregnancies with prenatal diagnosis of TS. Prenatal karyotype should be reevaluated postnatally (29, 30) owing to the risk of misdiagnosis, especially in mosaic cases.

Postnatal testing

Karyotyping is done after birth on the basis of external and internal stigmata. The phenotype is varied in girls and women with TS, and so the indications for testing differ during life (Figure 5) and according to karyotype (Figure 6).

Most TS diagnoses are set in the first years of life. Indications for testing a newborn are webbed neck, swollen hands and feet, low hairline, low set ears, cardiac malformations such as coarctation of the aorta and left-sided cardiac defects.

In children and adolescents, the most common stigmata are short stature and retarded growth velocity and absence of pubertal development.
Introduction

In adult women, TS is suspected when secondary amenorrhea, premature ovarian failure, primary or secondary infertility or recurrent miscarriages are present (30).

When testing adult women loss of X-chromosomes due to age should be considered. Russell and co-workers reported a frequency of X-chromosome loss ranging from 0.07% at age <16 years to 7.3% in women above the age of 65 (31). They postulated that the X-chromosome loss is most probably due to ageing when the loss is around 10% in women above 42 years of age (30 cell counted). Genuine X-chromosome mosaicism as compared with age-related loss of X-chromosomes is difficult to determine and the phenotype of the woman must be taken into consideration if an older woman is to be diagnosed with TS.

Age at diagnosis

Age at diagnosis differs widely depending on karyotype, different numbers of stigmata and girls with 45,X monosomy karyotype are often diagnosed earlier in life because they often have more distinctive physical features, symptoms and malformations. In a Swedish study the median age at diagnosis was 9 years in girls with monosomy and 13 years in mosaics. (19) and in a Danish study the age at diagnosis was 13 years for 45,X females and 19 years for females with any other karyotype except for monosomy and isochromosomes (31). In the Swedish Genetic Turner Register most girls were diagnosed in the neonatal period (Figure 7).

Figure 5. Diagnosis of TS in different periods in life. Personal communication I Bryman.
Figure 6. The median age at diagnosis in TS according to karyotype from Stochholm et al., 2006 (32) is shown. Courtesy of CH Gravholt.

Figure 7. Age at diagnosis for women with Turner karyotype in Sweden. Data from the Swedish Genetic Turner Register.
Introduction

**Prevalence**

Turner karyotypes are common among foetuses, but the live birth rate of newborns with TS karyotype is much lower, owing to spontaneous abortions and to some extent also to induced abortions. Monosomy 45,X foetuses do not survive the pregnancy to the same extent as mosaic fetuses (33, 34). In a study by Hook, the rate of survival of foetuses with 45,X diagnosed prenatally in the mid trimester, was only 25% vs. mosaic foetuses, in which the survival rate was almost 90%. In live born girls, TS is found in approximately 22 (Hook and Warburton 1983) to 50 per 100 000 girls (17, 35). In a Danish study from 2006, 40 TS per 100,000 females per year was diagnosed among girls born from 1970-1980. Since 1980 fewer girls with TS were diagnosed yearly. The authors suggest that with a delay of diagnosis of up to 30 years, most women with clinical symptoms will gradually be diagnosed, anticipating a true prevalence of 50 TS per 100 000 at birth (32).

**Morbidity in TS**

Morbidity in women with TS is overall increased. The severity of morbidity often depends on the karyotype, the monosomy, 45,X karyotype representing the most severely affected women and the low-grade mosaic karyotype representing more healthy TS women.

**Cardiovascular diseases**

Aortic dilation is often seen and aortic dissection is a risk for women with TS. The highest risk for aortic dissection is among women with risk factors such as 45,X, cardiac malformations, hypertension, aortic dilation and during pregnancy. However, aortic dissection do occur in women with no known risk factors and at a young age (36-38). The standardized mortality ratio (SMR) for aortic aneurysm is 23.6, (95% CI 13.8-37.8) according to a study from Great Britain in 2008 (39). The mechanism of aortic dissection in women with TS is still not known, but a high frequency of cystic medial necrosis or degeneration has been reported in women with aortic dissections as well as altered elastin fiber composition (40, 41). Disturbances in the medial layer of the arterial walls may be caused by primary defects in the extracellular matrix or abnormal tissue homeostasis but the aetiology is not fully understood (42).

Prevalence of hypertension is elevated increased in TS and three times more common than in healthy females (43). This is seen even at young ages. The diurnal blood pressure profile was found to be abnormal by Nathwani and co-workers (2000), who reported that a prevalence of over 30% of TS girls aged 5-22 years were mildly hypertensive (44). Hypertension is a major risk factor for aortic dilation (41) and for other cardiovascular diseases seen in Turner women.
Other cardiovascular disease such as ischaemic heart disease is frequent and could be an effect of central obesity, insulin resistance or hypercholesterolemia, that are often seen in TS women (45) or because of the oestrogen deficiency. Whether hormone replacement therapy (HRT) in TS women is protective in relation to ischemic heart disease is unclear, but it is suggested to have beneficial effects on arterial central hemodynamics and insulin sensitivity, and to have effects on the endothelial function. (46, 47). Long term effects of HRT remain to be evaluated.

Endocrine disease
Hypothyroidism is common in TS. In a Swedish study from 2005, 25% of women with TS had hypothyroidism, as compared with 2% in the general population. In a five year follow-up of the same women, 37% had hypothyroidism (48). The yearly incidence of autoimmune hypothyroidism was 3.2%, with no difference in incidence according to karyotype. Therefore it is advisable to test thyroid function regularly. Autoimmunity as a cause of hypothyroidism has previously been reported by Elsheikh 2001 and later in 2009 by Mortensen (49, 50).

Diabetes type 2 and glucose intolerance are being four times more common in women with TS than in the general population and is related to more body fat and overweight, commonly found in TS (43, 51).

Cancer
The overall risk of cancer is not elevated, but certain diagnoses were seen more often in women with TS; gonadoblastoma, meningioma and childhood brain tumours (43, 52, 53). A decreased risk of breast cancer was also seen.

Other morbidity
Autoimmune disorders are generally more common in women with TS and the incidence of gastrointestinal diseases such as celiac disease and inflammatory bowel disease is also increased in TS (54). Elevated liver enzymes levels are common in women with TS, with a prevalence of 36% at the age of 33, as reported in a study from Sweden (55). In a British study, the liver enzymes were higher in women with TS as compared with both controls and other women with premature ovarian insufficiency (56). In women with TS 91% demonstrated liver enzymes elevation. The reason for this elevation is not clear, but it is not an indication to stop HRT treatment.
Owing to short stature, growth hormone is administered during childhood and adolescence promoting growth and bone mass. Bone mineral content is lower in TS and could lead to osteoporosis and risk for fractures which was frequent among old women with TS. HRT and growth hormone treatment seemed to be protective (51, 57, 58).
Introduction

Mortality in TS

Women with TS have three times higher mortality, and reduced life expectancy than women in the general population. Life is reduced by over a decade. Cardiovascular diseases are the main cause of this raised mortality, and accounts for more than 40%, with aortic aneurysms and aortic valve disease as the most common diagnosis (39). In a Danish study, SMR was 2.1 for mosaic and other karyotypes, 3.9 for isochromosomes and 4.1 for 45,X (32).

Reproduction and fertility

Ovarian failure in TS

Ovarian insufficiency is one of the most common signs of TS and an important issue for affected women. The ovaries in foetuses with TS appear to be normal at eighteen weeks of gestation (59), after which the ovarian failure seems to begin in utero. Growth and formation of ovarian follicles are diminished, and acceleration of apoptosis leads to ovarian insufficiency at variable ages for the affected girls. The normal process of involution of oocytes that begins in utero and ends at menopause at the age of 50, with substitution of fibrous tissue for oocytes being accelerated in girls with TS. In many of the girls the process is completed at the time of birth or in the first few years in life. Ovaries convert to fibrous stromal streaks. The process varies, and there are TS girls with ovarian function and the possibilities of puberty and fertility, but they are rare (59-62). However, in a few cases the gradual loss of oocytes may last up to 40 years (63).

Ogata and Matsuo (1995) postulated that gonadal dysgenesis may depend on chromosome pairing failure during meiotic prophase in oocytes, causing oocyte loss. Severe pairing failure cause degeneration of the oocytes before puberty leading to primary amenorrhea and poor secondary sexual development. If the pairing failure is mild this may result in survival of oocytes until puberty, and a later high risk of infertility and premature ovarian failure. Pregnancy is not to be excluded in cases with mild pairing failure (64). The X-chromosome and deletions important for ovarian failure is shown in figure 8.

Ovarian insufficiency or failure and diminished ovarian feedback result in elevated levels of follicle stimulating hormone (FSH) and luteinizing hormone, increasing to menopausal levels in early adult life. FSH and inhibin B can be used as markers of remaining ovarian function. Inhibin B is secreted by developing follicles (65). Anti-Müllerian hormone (AMH) is a promising marker of ovarian function in girls with TS, screened for ovarian failure. Hagen and co-workers reported that if AMH was less than 8 pmol/liter the sensitivity was 96% and specificity 86% for ovarian failure (66).
**Puberty in TS**

Most girls with TS need induction of puberty. Pubertal induction usually begins with low-dose transdermal oestrogen treatment between the age of 12 and 14, with increasing doses during the following 2-3 years. HRT should begin at normal pubertal age and continue until normal menopausal age, 50-55. Oestrogen replacement is also considered important to be able to preserve bone mass and decrease the risks of osteoporosis and fractures (57, 58).

There is a small group of TS girls with spontaneous onset of puberty (5-16%), mostly mosaic girls. Breast budding and pubic and axillary hair appear in 5-25% of patients and menstrual cycles in 2-5 % before the onset of premature menopause (61, 67). In 1990, Massa reported spontaneous puberty in 17 cases of 100 girls with TS, 10 experienced menarche (mean age for menarche 14.3 (range 13.7-15.2 years) (68). It was noted that TS girls with Xp disomy had more spontaneous puberty and were taller. The region Xq13-q26 is thought to contain the genes responsible for ovarian function, and it apparently remain intact in girls who shows...
some signs of puberty. An Italian study reported that some pubertal signs could be seen in 50% and complete pubertal development in 16% of a cohort of TS girls and women. Only 5% in the group with 45,X had spontaneous puberty (69). These data were confirmed by Hagen with 6% spontaneous pubertal signs in 45,X and 54% in miscellaneous karyotypes. Ovarian failure was predicted using undetectable inhibin B and 10% of the girls entered puberty (65).

TS girls or women with normal sexual development are often diagnosed later in life on the basis of infertility or premature ovarian failure and most of them have a mosaic karyotype.

**Fertility in TS**

The chance of spontaneous pregnancy is reduced and occurs almost exclusively in women with mosaic karyotype, although there are some published case reports about women with monosomy 45,X karyotype as well as pregnancies in a woman with Y-fragment (70-73). Spontaneous pregnancies have been found to occur in 2-8% of all women with Turner karyotype (23, 67, 74, 75). In a Danish nationwide study 8 % (n=31) of all known women with TS had at least one spontaneous pregnancy (75). No woman with a spontaneous pregnancy had a monosomy karyotype.

Miscarriages are frequent in spontaneous pregnancies and according to some studies also in pregnancies achieved through oocyte donation (OD treatment) (76). In a Swedish study from 2011, an increased incidence of miscarriages was noted in spontaneous pregnancies, 45%, as compared with 26% in OD (67).

This is partly explained in terms of small uterine size and reduced endometrial receptivity (23, 76-78), although uterine development is normal. The question whether the risk of miscarriages is increased in spontaneously conceived pregnancies because of chromosomal abnormalities have been discussed. Transmission of a Turner karyotype from mother to daughter has been reported in several studies (23, 24, 79).

**Oocyte donation in TS**

The first delivery after OD was reported in 1984 by Lutjen and co-workers (80) and for most women with TS, assisted reproductive technologies (ART) have been encouraging, concerning the possibility of having children of their own. Childbearing is desired by most Turner women, and for many women with TS, OD is the best option owing to the early ovarian insufficiency. OD is an option in many countries today, and has been allowed in Sweden according to the legislation since 2003. In Denmark and Finland OD has been allowed since 1992. Pregnancy rates after OD in women with TS are reported to be the same
as or similar to those observed in other groups of oocyte recipients (76, 81), although poor results also have been reported (82).

**Other assisted reproductive technologies**

Cryopreservation of ovarian tissue and retransplantation is now possible and might be a future option for girls and women with TS (83, 84). This technique could be used if there is enough ovarian tissue in a young girl to take biopsies from for use in the future. Borgström et al. reported that ovarian biopsy was feasible in 47 of 57 girls with TS, aged 8-19.8 years. In 26% (15/57) follicles were identified in the tissue. There are several ethical considerations about this treatment. The biopsy has to be taken when the girl is young and cannot understand the risks and consequences.

In 2011, Donnez et al., reported successful allografting of ovarian cortex between two monozygotic twins both affected by TS (45,X/46,XX mosaic) with discordant ovarian function. The sister with the transplanted ovarian cortex gave birth to a healthy girl after spontaneous conception and normal pregnancy 16 months after transplantation. The donating sister had had two healthy children after spontaneous pregnancies (85).

Oocyte cryopreservation is the most promising future technique for TS girls with spontaneous puberty and signs of ovarian function (61). Case reports have been published about successful controlled ovarian stimulation and oocyte cryopreservation in TS patients (86, 87).

**Obstetric outcomes in TS**

Pregnancy outcomes have mainly been described in case reports and there are few large studies.

The complication rate during both spontaneous and OD pregnancies for TS women is elevated because of the high risk of hypertensive disorders and pre-eclampsia. Some studies report hypertensive complications in 36-63% of TS patients (37, 38, 76, 88, 89).

The most important and striking risk in Turner pregnancies is the risk of death from aortic dissection with a described mortality risk of 2% (36, 38). In the study by Karnis et al., 258 clinics with OD programs in the USA were contacted and 44% responded, reporting 101
pregnancies in 146 women with TS. A literature review in the same time period found 4 deaths due to aortic dissection in pregnant women with TS resulting in a 2% mortality rate. In a French study, a retrospective evaluation of 93 OD pregnancies in women with TS was done and two of the women had died from aortic dissection (38).

Risk factors for aortic dissection in TS are coarctation of the aorta, BAV, hypertension and aortic dilation, all seen in high frequencies in TS women (90). During pregnancy the risk is amplified because of the normal physiological changes and pregnancy-related hypertensive disorders.

**Table 1.** Life threatening complications and maternal deaths during pregnancy in patients with TS: literature review. (Modified after Alvaro Mercadal *et al.*, 2011).

<table>
<thead>
<tr>
<th>Affection</th>
<th>Reported deaths</th>
<th>Time of aortic dissection</th>
<th>Time of death</th>
<th>Type of pregnancy</th>
<th>Newborn outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nagel, 1997</td>
<td>2 Ao Diss</td>
<td>Third trimester</td>
<td>Third trimester</td>
<td>OD</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Garvey, 1998</td>
<td>1 Ao Diss</td>
<td>24 gw</td>
<td>88 days after CS</td>
<td>OD singleton</td>
<td>Healthy</td>
</tr>
<tr>
<td>Weytjens, 2000</td>
<td>1 Ao Diss</td>
<td>2 weeks after CS for eclampsia</td>
<td>NA</td>
<td>Spontaneous</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Beauchesne, 2001</td>
<td>1 Ao Diss</td>
<td>36 gw</td>
<td>36 gw</td>
<td>OD (triplets reduced to twins)</td>
<td>Ventilation required and seizure activity</td>
</tr>
<tr>
<td>Landin, 2004</td>
<td>1 Ao Diss</td>
<td>7th month of pregnancy</td>
<td>Alive</td>
<td>Spontaneous Singleton</td>
<td>Healthy</td>
</tr>
<tr>
<td>Gravholt, 2006</td>
<td>1 Ao Diss</td>
<td>1 year after pregnancy</td>
<td>1 year after pregnancy</td>
<td>OD twins</td>
<td>Healthy</td>
</tr>
<tr>
<td>Boissonnas, 2009</td>
<td>1 Ao Diss</td>
<td>38 gw</td>
<td>16 h after repair</td>
<td>OD singleton</td>
<td>Healthy</td>
</tr>
</tbody>
</table>
| Chevalier, 2009 | 1 cardiac failure after severe PE | 27 gw | NA | OD twins | Twin 1: Hyaline membrane disease, bronchopulmonary dysplasia  
Twin 2: Neuromotor troubles |
| Ohl, 2008/ Fénelon, 2010 | 1 Ao Diss | 39 gw | 7 days after CS | OD | Unavailable |

Ao Diss aortic dissection, gw gestational week
To our knowledge, eight cases of aortic dissection have been reported in women with TS who were pregnant (or within one year after delivery). Only two survived (37) (Table 1). Dissection has been seen both during and shortly after pregnancy. Two pregnancies were twin pregnancies after OD.

In Sweden, an incidence of aortic dissection during pregnancy was reported to be 14.5/1,000,000 between 1987 and 2007 (91). There were nine maternal deaths (4.4/1,000,000) because of aortic dissection. Five cases were described in more detail; however, none of the women had a diagnosis of TS. Pregnancy was found to be associated with a 25-fold increased risk for aortic dissection among young women (90).

In general, OD pregnancies are associated with a two to threefold higher risk of complications than conventional IVF (92-95). These pregnancies are associated with a high incidence of first trimester bleeding and a two to threefold higher risk of gestational hypertension and pre-eclampsia as compared with conventional in vitro fertilization (IVF).

When comparing OD treatment in women with TS and women applying for OD for other reasons, the risk of gestational hypertension and pre-eclampsia are very similar (93, 96, 97). The incidence of hypertensive disorders in pregnancy in general is 6 to 8%. A recent meta-analysis of 28 studies found a rate of hypertensive disorder of 22.6% after OD in general. The OR for developing a hypertensive disorder after OD compared with ART with own oocytes was 2.57 (95% CI 1.91 to 3.47) and compared with spontaneous conception 6.60 (95% CI 4.55 to 9.57) (98). The effect was independent of maternal age and multiple pregnancies. The reason for increased hypertension in OD is not fully understood but could be attributable to ovarian dysfunction and immunological factors causing placental pathology (99).

Complications in pregnancies after OD as compared with spontaneous pregnancies in TS have not been studied, nor has the question whether risks are increased for women with TS of a specific karyotype. These studies are difficult to perform owing to the very small number of affected women. For this reason, case reports must be considered for review. Most women with TS are delivered by caesarean section; because of short stature and fetopelvic disproportion. Spontaneous vaginal deliveries occur but are infrequent. See table 2 on pregnancies in women with TS.
Table 2. Studies reporting obstetric and neonatal outcomes in women with Turner syndrome. Studies with only one or two case reports were excluded.

<table>
<thead>
<tr>
<th>Author, country, study design, year of publication</th>
<th>Women, pregnancies, deliveries</th>
<th>Mode of conception</th>
<th>Miscarriages</th>
<th>Children</th>
<th>Gestational hypertension</th>
<th>Pre-eclampsia</th>
<th>IUGR</th>
<th>PTB</th>
<th>IUFD</th>
<th>Malformations or chromosomal aberrations</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tarani et al., Italy Literature review including six own cases, 1998</td>
<td>74 / 160 / 93</td>
<td>NA</td>
<td>29% (47/160)</td>
<td>94 live newborns (92 singletons, 2 twins) + 9 with no information</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>7% (11/160)</td>
<td>34% (32/94, 21/32 TS or trisomy 21)</td>
<td>15 TS mothers gave birth to 15 TS daughters</td>
</tr>
<tr>
<td>Own case-reports, 1998</td>
<td>Own case-reports, 1998</td>
<td>6 (included above)</td>
<td>6 SC</td>
<td>NA</td>
<td>8 (6 singletons 2 twins)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>50% (4/8)</td>
</tr>
<tr>
<td>Foudila et al., Finland Retrospective study, 1999</td>
<td>18 / 20 / 11</td>
<td>OD</td>
<td>NA</td>
<td>12 (10 singletons+ 2 twins)</td>
<td>NA</td>
<td>54.5% (6/11)</td>
<td>1</td>
<td>9% (1/11) (twin)</td>
<td>0</td>
<td>0</td>
<td>1 hysterectomy (severe bleeding in a twin pregnancy)</td>
</tr>
<tr>
<td>Birkebaek et al., Denmark, Register based study, 2002</td>
<td>33 / 7 / 61</td>
<td>31 SC 2 ART (1 OD)</td>
<td>NA</td>
<td>64 (58 singletons+ 6 twins)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>9% (6/64 including 3 siblings)</td>
<td>No maternal death</td>
</tr>
<tr>
<td>Karnis et al., USA, Retrospective study and literature review, 2003</td>
<td>146 / 101 / 94</td>
<td>OD</td>
<td>NA</td>
<td>NA (16.8% twins)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>49.3% cardiac prescreened, 6 with abnormal result Estimated maternal mortality rate of 2%</td>
</tr>
<tr>
<td>Bodri et al., Spain Retrospective study, 2006</td>
<td>21 / 17 / 8</td>
<td>OD (9 after 12 weeks, one not delivered)</td>
<td>47%</td>
<td>9 (7 singletons+ 2 twins) (1 triplet reduced to singleton)</td>
<td>62.5% (5/8)</td>
<td>37.5% (3/8)</td>
<td>55.5% (5/9)</td>
<td>50% (4/8)</td>
<td>11% (1/9) (33 gw, pre-eclampsia)</td>
<td>0</td>
<td>All women cardiac prescreened. One had mild aortic insufficiency and 1 chronic hypertension</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Study Design</td>
<td>Sample Size</td>
<td>OD</td>
<td>SC</td>
<td>OD/SC</td>
<td>Outcome 1</td>
<td>Outcome 2</td>
<td>Outcome 3</td>
<td>Outcome 4</td>
<td>Outcome 5</td>
</tr>
<tr>
<td>------------------------------</td>
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<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>Bodri et al., Spain</td>
<td>Spain</td>
<td>Retrospective case/control</td>
<td>29</td>
<td>OD</td>
<td>7</td>
<td>1</td>
<td>86% (6/7)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alvaro Mercadal et al.,</td>
<td>Belgium</td>
<td>Retrospective case reports</td>
<td>23 29</td>
<td>OD</td>
<td>18</td>
<td>10</td>
<td>44% (8/18)</td>
<td>11</td>
<td>10% (1/10)</td>
<td>40% (4/10)</td>
<td>40% (4/10)</td>
</tr>
<tr>
<td>Bryman et al., Sweden</td>
<td>Sweden</td>
<td>Retrospective multicenter</td>
<td>57 57</td>
<td>OD</td>
<td>124</td>
<td>67</td>
<td>45% (37/82)</td>
<td>68</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Chevalier et al., France</td>
<td>France</td>
<td>Retrospective multicenter</td>
<td>93 93</td>
<td>OD</td>
<td>82</td>
<td>67</td>
<td>90 with known outcome, 87 healthy newborns (8.6% twin pregnancies)</td>
<td>17% (14/82)</td>
<td>20.7% (17/82) including 3 with eclampsia and 1 HELLP</td>
<td>27.5% (14/51) (&lt;10th centile)</td>
<td>38.3% (28/73) (&lt;35 gw)</td>
</tr>
<tr>
<td>Hadnott et al., USA</td>
<td>USA</td>
<td>Case reports</td>
<td>10 10</td>
<td>SC</td>
<td>13</td>
<td>13</td>
<td>14 (12 singletons+2 twins (OD))</td>
<td>0</td>
<td>0 in SC</td>
<td>0 in SC</td>
<td>0 in SC</td>
</tr>
</tbody>
</table>

PTB preterm birth, IUGR intrauterine growth retardation, SC spontaneous conception, ART assisted reproductive technologies, BAV bicuspid aortic valves, CS Cesarean section, NA not available, gw gestational weeks, TTTS twin-twin transfusion syndrome, HELLP hemolysis, elevated liver enzymes and low platelets
Introduction

Neonatal outcomes in TS

Neonatal outcomes in women with TS are presented in table 2. The incidences of intrauterine growth restriction, preterm birth and birth defects in OD in the general population have mostly been comparable with conventional IVF (94) although impaired foetal growth in OD pregnancies as compared with conventional IVF has been noted (100). In Turner women treated with OD, rates of preterm birth have ranged from 30-50% and small for gestational age (SGA) from 27-40% (37, 38, 88). None of these studies used control groups.

The high rate of preterm births and SGA could to some extent be explained by the higher incidence of hypertensive disorders in Turner OD pregnancies.

Stillbirths and malformations have been reported to occur in high frequencies in Turner women, but most reports are case reports (23). In the report by Tarani et al., 15/94 children had TS and, 4/94 trisomy 21. Birkebaek noted six children, three of whom were siblings, with chromosome aberrations out of 64 children in 33 women, as well as two children affected by malformations (75). In Sweden, birth defects or serious illness were found in 7% (5/68, 2 birth defects, 3 other serious disorders) in a study of 68 children of women examined at Turner centers at University hospitals (67).

International and national guidelines

Karnis and co-workers found in a study from 2003 that only half of women with TS in the United States had had a cardiac examination before fertility treatment (36). Consequently, the American Society for Reproductive Medicine (ASRM) has introduced specific recommendations for screening and management of women with TS before and during pregnancy (101, 102). They state that:

- TS is a relative contraindication for pregnancy
- Cardiology and maternal-foetal medicine consultation for evaluation and careful screening are required before considering pregnancy by OD
- Cardiac magnetic resonance imaging (MRI) revealing any significant abnormality and/or aortic size index (ASI) >20 mm/m² represents an absolute contraindication for attempting pregnancy in woman with TS
- Women with TS having a normal cardiac MRI and evaluation who decide to attempt pregnancy after thorough counselling are still at much higher risk for associated morbidity and mortality and require careful observation and frequent formal re-evaluation throughout gestation and postpartum
After deaths due to aortic dissections in two TS women following OD, French guidelines were published in 2010 at the request of the Directorate of the French Biomedicine Agency (103), recommending thorough cardiac evaluation before OD in women with TS. In addition to the requirements in the American guidelines, magnetic resonance angiography of the heart and aorta is mandatory. As contraindications the French guidelines state:

- An ASI $\geq 25$ mm/m² or above 35 mm should be considered as a dilated ascending aorta with risk of dissection
- A history of aortic surgery
- A history of aortic dissection
- Aortic coarctation
- Uncontrolled hypertension despite treatment
- Portal hypertension oesophageal varicose veins

The guidelines do not state that isolated bicuspid aortic valve (without aortic dilation) is a contraindication to pregnancy, but it is a risk factor.

The French guidelines also recommend close and careful follow-up during pregnancy and after pregnancy. Any pregnancy in women with TS, OD or not, must be reported to the Turner Syndrome Registry in France.

In Sweden, the Swedish Turner Academy has published guidelines concerning health care programme for women with TS (104) in general including recommendations for women with TS who become pregnant.

- Pregnancy is not recommended in women with cardiac anomaly (coarctation or BAV or other serious defect)
- The pregnancy should be followed up at a specialized antenatal clinic and by a specialized cardiologist
- MRI should be performed to evaluate any cardiac defect and aortic size, before pregnancy
- Prenatal screening and amniocentesis should be offered and discussed in women with TS and spontaneous pregnancy

Women with congenital cardiac anomalies, with or without previous surgery, are not recommended pregnancy.
Ethical considerations

Women with TS, like most other women, wish to have children and a family. Involuntary childlessness lowers quality of life for these women and the happiness of being a mother justifies the hardships of going through treatments and sometimes complicated pregnancies and deliveries. Today, the possibilities of treating infertility are almost endless and research is being performed in wide areas relating to ART. Future possibilities in this area include freezing oocytes, ovarian tissue, and transplantation of ovary or uterus.

The question arises, however: who is responsible for pregnancy treatments that affect or increase morbidity or even threaten the lives of women who become pregnant or the unborn child? The doctor? The woman?

There are four ethical principles:
- The individual’s autonomy
- to do good
- not to harm
- justice

- and in addition there are relevant aspects of solidarity and integrity.

Treatment should not violate the individual or his or her integrity, should be positive, should not do any harm and should be justified in relation to other individuals and benefit for society. In treating women for infertility, most of these principles are complied with ethical dilemmas that must be considered when the treatment could do harm. This is a difficult issue, but must be addressed when a physician treats women with TS who wish to have a child.
Aims of the thesis

The overall aim of this thesis was to study characteristics of mothers of girls with Turner karyotype and to analyze morbidity and mortality in relation to childbirth and neonatal outcomes in women with Turner karyotype.

The specific aims were:

Paper I  to identify maternal characteristics in women who gave birth to girls with Turner syndrome and to describe the newborns with Turner syndrome, as compared with the general population.

Paper II  to study obstetric and neonatal outcomes in women with Turner karyotype who had given birth as compared with women and children from the general population.

Paper III to study obstetric and neonatal outcomes after oocyte donation in women with Turner syndrome in three Nordic countries, Finland, Denmark and Sweden, and to study pre-pregnancy cardiac evaluations and morbidity.

Paper IV to study morbidity and mortality in the years after childbirth in women with Turner karyotype, with special emphasis on cardiovascular disease, as compared with women with Turner karyotype without childbirth and a reference group from the general population.
Material and Methods

Ethics approval

All the studies were approved by the regional Ethics Committee in Gothenburg. Paper III was approved by the Ethics Committee of Gynaecology and Obstetrics, Paediatrics and Psychiatry, Hospital district of Helsinki and Uusima, Finland and in Denmark paper III was approved by Danish Data Protection Agency and the Danish National Board of Health. All participants in Paper III gave their written consent before inclusion.

Study settings, patients, control groups and main outcomes

Karyotypes for the study populations in papers I-IV are presented in table 3 (Paper I-IV). The study settings, patients, control groups and main outcomes are presented in table 4 (Paper I-IV).

An overview of study populations, control groups and timeline is presented in figure 9 (Paper I-IV)

Table 3. Subgroups of karyotypes in girls and women with TS (Paper I-IV).

<table>
<thead>
<tr>
<th>Study population</th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper III</th>
<th>Paper IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Girls with Turner karyotype</td>
<td>Women with Turner karyotype, singletons</td>
<td>Women with Turner karyotype, all including twins</td>
<td>Women with TS and childbirth after OD</td>
</tr>
<tr>
<td>All, n</td>
<td>494</td>
<td>112</td>
<td>106*</td>
<td>502</td>
</tr>
<tr>
<td>Monosomy 45,X, n (%)</td>
<td>221 (44.7)</td>
<td>10 (8.9)</td>
<td>44 (44.0)</td>
<td>180 (35.9)</td>
</tr>
<tr>
<td>Mosaicism 45X, 46XX, n (%)</td>
<td>62 (12.6)</td>
<td>38 (33.9)</td>
<td>16 (16.0)</td>
<td>79 (15.7)</td>
</tr>
<tr>
<td>Isochromosome 45.X/46,Xi(X) 46,Xi(X), n (%)</td>
<td>78 (15.8)</td>
<td>Included in other</td>
<td>Included in other</td>
<td>Included in other</td>
</tr>
<tr>
<td>Other*, n (%)</td>
<td>133 (26.9)</td>
<td>52 (46.4)</td>
<td>52 (45.2)</td>
<td>223 (44.4)</td>
</tr>
<tr>
<td>Low-grade mosaicism**, (%)</td>
<td>NA</td>
<td>12 (10.7)</td>
<td>40 (40.0)</td>
<td>21 (4.2)</td>
</tr>
</tbody>
</table>

* Other including 45,X/46,XY 45,X/47,XXX 45.X/48,XXXXX 45.X/49,XXXXX, 45.X/51,XXXXX 45.X/46,der(X) (including ring chromosomes, deletions and translocations)
** Less than 6% 45,X in mosaicism 45.X/46,XX
# Exact karyotype unknown in 6 women
Table 4. Study settings, patients and main outcomes.

<table>
<thead>
<tr>
<th>Setting</th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper III</th>
<th>Paper IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Retrospective register study</td>
<td>Retrospective register study</td>
<td>Retrospective descriptive cohort study</td>
<td>Retrospective register study</td>
</tr>
<tr>
<td>No of newborns</td>
<td>494 girls with TS karyotype (483 singletons, 11 twins) born 1973 to 2005</td>
<td>208 (202 singletons, 6 twins)</td>
<td>131 (113 singletons, 18 twins)</td>
<td>NA</td>
</tr>
<tr>
<td>Control group</td>
<td>All other girls born 1973 to 2005 and their mothers n=1 610 754 girls</td>
<td>56 000 women (500/ woman with Turner karyotype, matched for year of birth) and their newborns (112 330 singletons)</td>
<td>No</td>
<td>(1) 378** women with Turner karyotype and no childbirth (2) 1230** women from MBR (10/woman with Turner karyotype and childbirth, matched for maternal age, number of children and year of birth of first child)</td>
</tr>
<tr>
<td>Cross-linkage</td>
<td>Swedish Genetic Turner Register, MBR</td>
<td>Swedish Genetic Turner Register, MBR, NPR, The Cause of Death Register, Register of Congenital Malformations</td>
<td>No</td>
<td>Swedish Genetic Turner Register, MBR, Cause of Death Register, NPR, Cancer Registry</td>
</tr>
</tbody>
</table>

**Main Outcomes**

<table>
<thead>
<tr>
<th>Setting</th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper III</th>
<th>Paper IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal</td>
<td>Karyotype, age, parity, height, BMI, smoking, endocrine diseases, diabetes, chronic hypertension, preeclampsia, placental abruptio, placenta previa, aortic dissection, maternal mortality</td>
<td>Karyotype, age, parity, height, BMI, smoking, endocrine diseases, diabetes, chronic hypertension, cardiac evaluation before and during pregnancy, preeclampsia, placental abruptio, placenta previa, aortic dissection, maternal mortality</td>
<td>Karyotype, age, parity, height, BMI, smoking, endocrine diseases, diabetes, chronic hypertension, cardiac evaluation before and during pregnancy, preeclampsia, placental abruptio, placenta previa, aortic dissection, maternal mortality</td>
<td>Karyotype, mortality, diseases of the circulatory system, malformations of the heart and kidney, endocrine diseases, gastrointestinal diseases, epilepsy, osteoporosis, cancer</td>
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<td>Neonatal</td>
<td>Gestational age: (weeks): &lt;28, 28-31, 32-36, 37-41, 42+</td>
<td>Mode of delivery</td>
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<td>SD weight and length: &gt;2, 2 to – 1, -1 to 1, 1-2, &gt;2</td>
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<td>Apgar score</td>
<td>Birth defects</td>
<td>Mortality (stillbirth or infant mortality up to 1 year of age)</td>
<td>Birth defects</td>
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TS Turner syndrome, NA not applicable, MBR medical birth register, NPR national patient register, BMI body mass index, PTB preterm birth, LBW low birth weight, SGA small for gestational age, LGA large for gestational age, SD standard deviation

* 11 women were also included in Paper II
** one woman with Turner karyotype and childbirth not included in MBR was found in NPR, therefore the MBR control group consisted of 1230 women
### Timeline of Study

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<td>Girls with Turner syndrome born 1973-2005, n=494</td>
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<td>Control group from Swedish Genetic Turner Register</td>
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<td>Control group from MBR</td>
<td>10 women from MBR/woman with Turner karyotype and childbirth, born 1957-1987 and childbirth 1973-2010*, n=1230</td>
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**Figure 9.** Timeline for study populations.

MBR Swedish Medical Birth Register

* Matched for year of birth

** Matched for maternal age, number of children and year of birth of first child
Material and Methods

Registers (Papers I, II and IV)

The Swedish Genetic Turner Register was created for research purposes and with ethics committee approval. Data were collected between 2000 and 2007 and include all girls and women with postnatal diagnoses of Turner karyotype between 1967 and 2007, incomplete for 2007. Data were collected from all Swedish cytogenetic laboratories (Göteborg, Linköping, Lund, Skövde, Stockholm, Umeå and Uppsala). The register includes data on analyzing laboratory, date of birth, information on karyotype and date of diagnosis. Only women with complete Swedish personal identification numbers were included in the present studies. Chromosomal analysis was mainly performed on cultures of peripheral blood lymphocytes. In some cases the analysis was also performed in fibroblasts and on buccal cells. In the majority of cases the number of counted cells was recorded. Between 1967 and 1994 Turner karyotype diagnosis was based on an analysis of 10-25 cells, while after 1994 at least 30 cells were analyzed.

Turner karyotypes were divided into following subgroups in the register (Figure 10).
1. Monosomy 45,X (n=338, 39%)
2. Mosaic 45,X/46,XX (n=134, 16%)
3. Isochromosomes 45,X/46,X,i(X) and 46,X,i(X) (n=103, 12%)
4. Ring chromosome 45,X/46,Xr(X), 45,X/46,XY, 45,X/46XmarY, 45,X/46del(X), 46,Xdel(X), other including 45,X/multiple X, 45,X/46,X t(X:X) (n=241, 28%)
5. Low-grade mosaic (less than 6% 45,X) (n=44, 5%)

Figure 10. Distribution of different karyotypes in the Swedish Genetic Turner Register (n=860).
Age at diagnosis ranged from 0-85 years, median age at diagnosis was 12 years.

Number of diagnosed women with Turner karyotype/year is shown in figure 11 and number of women with Turner karyotype born per year between 1916 and 2007 is shown in figure 12.

**Figure 11.** The Swedish Genetic Turner register with the number of women diagnosed with Turner karyotype/year, between 1967-2007 (n=860).

**Figure 12.** The Swedish Genetic Turner register and the year of birth for women with Turner karyotype (n=860).
No information regarding phenotype was available in the Swedish Genetic Turner Register. No validation has been done. Other limitations in the register are that the method for diagnosis was not standardized in this register, owing to different time periods, different tissues and due to different numbers of cells analyzed.

**Swedish Medical Birth Register**
The Swedish Medical Birth Register (MBR) was established 1973 and covers nearly all deliveries in Sweden, with only a very few percent missing (105). It contains information about maternal characteristics: age, parity, height, weight, socioeconomic status, smoking habits and information about antenatal care, delivery and neonatal data of live births and stillbirths. Data on smoking and maternal height have been registered since 1983. The Swedish definition of stillbirth between 1973 and June 30, 2008 was intrauterine foetal death after 28 completed weeks of gestation. Data on ART has been collected, although incompletely, since 1995. Data are collected prospectively from the first antenatal visit until after delivery including data on neonatal deaths in the first month of life. Validation occurs yearly by cross-linkage with the National Population Register (SCB) and the MBR, using the unique personal identification numbers of the mother and neonate.

The MBR was also evaluated by the National Board of Health and Welfare in 2002 [http://www.socialstyrelsen.se/publikationer2002/2002-112-4](http://www.socialstyrelsen.se/publikationer2002/2002-112-4). Data on pregnancies after ART has been marked in only 44% of women in the 2002 evaluation. Parity is well documented when the woman is not an immigrant, but in women who had childbirth abroad, the first birth in the MBR is mistakenly listed as the first child ever in as many as 11-12%, irrespective of how many previous births the woman had abroad. Pre-pregnancy maternal diagnoses have also been incorrectly documented. These diagnoses at the first antenatal visit are documented by marking a box for a) repeated urinary tract infections b) chronic disease of kidneys c) diabetes mellitus d) epilepsy e) asthma or pulmonary disease f) ulcerative colitis or Crohn’s disease g) systemic lupus erythematosus h) chronic hypertension. Diagnoses established at the maternity ward are better documented, with only a 1-2% margin of error. Data about infant birth weight and length is correct in more than 99%.

**The National Patient Register**
The National Patient Register (NPR) includes data from all Swedish hospitals beginning in 1987, and comprises date on hospitalizations and ICD codes (International Statistical Classification of Diseases and Related Health Problems) for each occasion from 1987. ICD-9 codes were used from 1987 to 1997 and ICD-10 codes from 1997. Since 2001, the NPR also contains outpatient appointments including day surgery and psychiatric appointments with both private and public caregivers. Primary care is not yet included in the NPR. Validation of
the NPR for inpatient diagnoses was performed in 2011. Overall, the positive predictive value was found to differ between diagnoses, but it was generally 85%-95%. No outpatient data were included in the present study. Both primary and other diagnoses were included in the study.

The Swedish Cancer Register
This register of cancers includes ICD codes and date of diagnosis from 1958. It is compulsory for every health care provider to report newly detected cases of cancer to the register. The register includes diagnosis of
1) all definitively malignant neoplasms,
2) carcinoid tumours, granulosacell tumours of the ovary,
3) in situ malignant tumours (i.e. lip, mouth, larynx, bronchus, trachea, cervix uteri, skin, vulva, vagina and ovarian cystadenoma),
4) certain benign tumours (the central nervous system, meninges, all hormonally active tumours of the endocrine glands).

Tumours are coded by site according to ICD. A code in the register classifies a tumour as benign or malignant.

A quality study of the register was made and published in 2008 (106). In it the coverage rate was evaluated in comparison with the NPR. Underreporting was estimated to be approximately 3.7%.

Cause of Death Register
The Swedish Cause of Death Register (CDR) includes all Swedish citizens who have died either in Sweden or abroad since 1952 and who were census registered in Sweden at the time of death. Causes of deaths are registered as ICD codes.

Register of Congenital Malformations
The register was established in 1965 to be able to see increases in malformations and to study changes in certain malformations over time. The register includes congenital malformations and chromosomal aberrations detected in the first month of life or congenital cardiac malformations within one year after birth. It includes induced abortions owing to prenatal screening and diagnosing since 1999, but without personal identification number. Malformations are described and reported as ICD codes. The quality of the register was evaluated in 2004 by the National Board of Health and Welfare (http://www.socialstyrelsen.se/publikationer2004/2004-112-2) and proved to be good. The register is validated annually against registers from the Swedish cytogenetic laboratories and the Medical Birth Register.
**Methods Paper I**

**Women who gave birth to girls with Turner syndrome: maternal and neonatal characteristics**

Paper I is a retrospective population-based controlled cohort study of all 494 women who gave birth to a live born girl with TS between 1973 and 2005. Data from the Swedish Genetic Turner Register was linked with the MBR via the unique personal identification number given to all Swedish citizens.

Karyotypes were divided into subgroups: monosomy 45,X, mosaic 45,X/46,XX, isochromosomes and ‘other karyotypes’.

The control group consisted of all other women and newborns in the MBR during the same time period.

Maternal age, parity, height, smoking habits in first trimester and mode of delivery were outcome measures for mothers.

Neonatal outcomes for girls with TS were gestational age at birth, weight and length at birth and Apgar scores. Weight and length at birth were calculated as standard deviations (SD) from expected mean birth weight and length according to gestational age and sex in a Swedish reference population (107).

**Methods Paper II**

**Obstetric outcomes in women with Turner Karyotype**

Paper II is a retrospective population-based controlled cohort study of all 115 women with a Turner karyotype who gave birth to a live born or stillborn infant between 1973 and 2007.

Data from the Swedish Genetic Turner Register was cross-linked with the MBR, the NPR, the Cause of Death Register and the Register of Congenital Malformations.

Karyotypes were divided into subgroups: monosomy, mosaic 45,X/46,XX, other karyotype and low-grade mosaic with less than 6% 45,X.

The control group consisted of 500 women per woman with Turner karyotype randomly selected from the MBR and matched for year of birth.
Material and Methods

Maternal outcomes were age, parity, height, body mass index (BMI), and smoking habits at first consultation in a primary care unit. The International Classification of Diseases (ICD) codes 8, 9, and 10 were used to study preexisting diseases such as endocrine diseases, diabetes, and chronic hypertension as well as complications during pregnancy such as pre-eclampsia, placental abruption, placenta previa, aortic dissection, and maternal mortality.

Neonatal outcomes were sex, mode of delivery, gestational week at delivery, weight and length at birth, Apgar scores, birth defects and mortality (stillbirth and neonatal and infant mortality up to 1 year of age). Weight and length at birth were calculated as SD from expected mean birth weight and length according to gestational age and sex in a Swedish reference population (107)

Twin outcomes were described separately.

Methods Paper III
Obstetric and neonatal outcome after oocyte donation in 106 women with Turner syndrome. a Nordic cohort study

Paper III is a retrospective descriptive cohort study of 106 women with TS who gave birth after OD in Finland, Denmark and Sweden between 1992 and 2011.

Written informed consent was obtained from the women, in all countries.

In Finland and Sweden all fertility clinics were contacted and asked to identify women with TS who had delivered after OD treatment. In Denmark all women with a delivery after OD and TS were identified by cross-linkage the Danish IVF Registry and the MBR using the Central Personal Registry (CPR) number and then linking the CPR numbers of the women with the Cytogenetic Central Register to obtain women with TS and exact karyotype.

In all countries, data regarding general health, obstetric and neonatal outcomes were collected from medical records of fertility clinics, obstetric and gynaecological hospitals and other relevant hospitals where the women had been treated. In Denmark diagnoses of the women with TS were first collected from the National Discharge Registry and perinatal data were then extracted from the MBR. Supplementary data were collected from the medical records.

Karyotypes were subgrouped into 45,X monosomy, 45,X/46,XX mosaics or other TS karyotype. In most cases of mosaicism, no information about the percentages of mosaic cell lines was available.

There was no control group.
Material and Methods

IVF/OD treatment did not differ greatly between countries. Matching of donors was done in Finland if possible, in Denmark no matching was done while the oocyte supply was far below demand and in Sweden donors were matched with recipient’s height, weight, eye and hair color if possible.

Recorded data and outcomes
The following maternal characteristics were recorded: karyotype, age at diagnosis, embryo transfer strategy, pre-existing diseases including congenital cardiac disease, pre-pregnancy (any time before pregnancy) and pregnancy cardiac examination, age at delivery, height, BMI and smoking habits at first antenatal visit, previous deliveries, pregnancy and delivery outcomes, and mode of delivery.

Neonatal outcomes included data on gestational age (determined according to the day of embryo transfer, which varied between day 16 and 19), preterm birth (PTB) (<37 weeks), very preterm birth (VPTB) (<32 weeks) extreme preterm birth (<28 weeks), birth weight, low birth weight (LBW) (<2500 g), very low birth weight (VLBW) (<1500 g), extreme low birth weight (ELBW) (<1000 g), small for gestational age (SGA), large for gestational age (LGA), low Apgar score (<7 at 5 minutes), admissions to neonatal intensive care units (NICU), birth defects (any Q codes according to the ICD 9 or 10) and perinatal mortality.

Methods Paper IV

Morbidity and mortality after childbirth in women with Turner karyotype
Paper IV is a retrospective population-based controlled cohort study of 124 women with Turner karyotype born between 1957 and 1987 and who gave birth between 1973 and 2010. Women born before 1957 were excluded because it was considered reasonable to include women below 30 years of age (not too old) at the time when the NPR was established in 1987. Women with Turner karyotype were identified in the Swedish Genetic Turner Register. Data were obtained by cross linkage to the Swedish MBR, the CDR, the NPR and the Swedish Cancer Register.

Karyotypes were divided into subgroups: monosomy 45,X, 45,X/46,XX mosaics, other karyotypes and low-grade mosaics (less than 6% 45,X).

Control group: Women with Turner karyotype without childbirth (n=378) from the Swedish Genetic Turner Register born during the same time period, 1957-1987 were selected as controls, without matching.
A second control group consisted of 10 women per woman with Turner karyotype and childbirth randomly selected from the Swedish MBR (n=1230) and matched for maternal age, number of children and year of birth of first child. One woman with TS and childbirth was not registered in the MBR but was identified in the NPR. The MBR control group therefore consisted of 1230 women.

Outcomes were the following diagnoses selected from the NPR (ICD 10), [ICD 9]: All diseases of the circulatory system (I00-I99), [390-459], hypertension (I10-I15), [401-405], ischaemic heart disease (I20-I25), [410-414], valvular disease (I33-I39), [421, 424], arrhythmia (I44-I49), [426-427], aortic aneurysm (I71), [441], cerebrovascular disease (I60-I69), [430-438], thromboembolic disease including pulmonary embolism (I26, I80-82), [415, 451-453], all heart malformations (Q20-Q26), [745-747], aortic coarctation (Q25.1), [747B] bicuspid aortic valve (Q23.1), [746E], all renal malformations (Q60), [753], all endocrine, nutritional and metabolic diseases (E00-E90), [240-279], diabetes mellitus (E10-E14), [250], all thyroid disease (E00-E07), [240-246], hypothyreosis (E03-E04), [240-241, 244], thyreotoxicosis (E05), [242], thyroiditis (E06), [245], all gastrointestinal diseases (K70-K93), [520-579], diseases of the liver (K70-K77), [570-573], diseases of the gallbladder and pancreas (K80-K87), [574-575], Crohn’s disease and ulcerative colitis (K50-K51), [555-556], epilepsy (G40-G41), [345] and osteoporosis (M80-M81), [733A].

Statistical methods
All statistical analyses in Paper I, II and IV were carried out in collaboration with Karin Källen, Associate Professor, Department of Reproduction Epidemiology, Tornblad Institute, Institute of Clinical Sciences, Lund University, Lund, Sweden.
All statistical analyses in Papers I, II and IV were performed using Gauss (Gauss TM, Aptech Systems Inc, Maple Valley, WA, USA, [http://www.aptech.com]), and in Paper III using a statistical software package (SPSS, PASW Statistics 18).

Statistics in Paper I
Women who gave birth to girls with Turner syndrome: maternal and neonatal characteristics
The aim of the study was to evaluate possible associations between Turner karyotype (and specified subgroups of Turner karyotype) and characteristics of mothers and infants. Associations were investigated using simple and multiple logistic regression analyses as specified: linear, quadratic and polynomial models were tested. The best available models were determined using visual inspection and the Hosmer-Lemeshow test for goodness of fit. Variables with P-values below 0.2 were included in the final models. The Odds Ratios (ORs)
Material and Methods

with 95% confidence intervals (CIs) obtained from the multiple logistic regression analyses were used to produce graphs. Tests of homogeneity of the ORs across strata were based on weighted sums of the squared deviations of the stratum specific log-ORs from their weighted means (Hosmer and Lemeshow, 1989). Continuous data were analysed with Kruskal Wallis non-parametric tests or ANOVA as specified. Findings with P-values below 0.05 were regarded as statistically significant.

Analysis was performed on all TS karyotypes combined and on subgroups of TS karyotypes (monosomy, mosaic, isochromosomes, others).

Statistics in Paper II

Obstetric outcomes in women with Turner karyotype

The aim of the study was to evaluate differences in obstetric and neonatal outcomes in women with Turner karyotype as compared with a reference population from the MBR. The control group was matched for year of birth, randomly selected. All other parameters from the MBR were included in the outcomes.

In singletons, maternal and infant outcomes of pregnancies in all women with Turner karyotype were compared with the corresponding outcomes among the reference group. Efforts were made to account for correlated outcomes for each woman, making it difficult with more than 500 controls/case. For binary outcomes, logistic regression analyses were performed, using Generalized Estimating Equation (GEE) technology to obtain robust variance estimations. For continuous outcome variables, the same technique was used to perform ANOVA analyses with robust variance estimations. Adjustments were made for maternal age at delivery (continuous variable, second grade model with one linear and one quadratic term), and parity (1,2,3 and 4+ as class variables). Continuous maternal characteristic data were analyzed using the Kruskal-Wallis test (test for heterogeneity within the TS group) and the Mann-Whitney U-test (test for difference between the Turner karyotype group and the reference group), respectively.

Data were presented as means (SD) and medians (range). Data on maternal characteristics were presented for all Turner karyotypes, for subgroups (monosomy, mosaic, others and low-grade mosaics) and for all Turner karyotypes excluding low-grade mosaics, respectively. Data on neonatal outcomes were presented for children born to women with any Turner karyotype and for children born to women with Turner karyotype excluding women with low-grade mosaicism.
Statistics in Paper III

Obstetric and neonatal outcomes after oocyte donation in 106 women with Turner syndrome: a Nordic cohort study

The aim of this study was to describe pre-pregnancy cardiac evaluation and morbidity before and during pregnancy and obstetric and neonatal outcomes after OD in TS women in Sweden, Finland and Denmark. This study was descriptive with no control group.

Data were presented as mean, SD, and median, range. Data were presented for all women and deliveries, for each country, for singletons and twins separately and for each karyotype. Selected outcomes in women with 45,X were compared with outcomes in women with a mosaic or other TS karyotype. Comparisons between continuous variables were performed with the Mann-Whitney U-test.

Statistics in Paper IV

Morbidity and mortality after childbirth in women with Turner karyotype

The aim of the study was to study morbidity and mortality after delivery in women with Turner karyotype.

Data were presented as median (range). Statistical analyses were performed on all Turner karyotypes and on a subgroup of all Turner karyotypes excluding women with low-grade mosaicism. Statistical analyses were performed on main outcomes, diseases of the circulatory system and on endocrine and gastrointestinal diseases. Cox analyses were performed in order to obtain hazard ratios (HR) (with 95% CI) for morbidity by age-strata, and timing in relation to pregnancy. Each outcome was only counted once for each woman.

When comparing the morbidity in women with Turner karyotype who had given birth with those who did not, stratifications were made <40 years, and 40 years or more, respectively. In these analyses, adjustments were made for the woman’s year of birth.

In the comparisons between women with Turner karyotype who had given birth and age- and parity-matched controls, the ‘time at risk’ for each woman was recorded by counting the number of days between different events:

1. Pre-pregnancy: for each outcome studied, the number of pre-pregnancy days at risk was counted from 1 January 1987, when the first in-patient data were obtainable, to the estimated first day of first pregnancy, or until the first diagnosis of certain outcome.
Material and Methods

2. During pregnancy and one year after each pregnancy: The number of days at risk were obtained by adding the duration of each pregnancy to 365 days after each delivery, or until the first diagnosis (for each outcome separately) if it occurred during pregnancy or within one year after.

3. More than one year after the first delivery: Excluding the days during any pregnancy and the year following each delivery, the number of days at risk were counted from the first delivery to the time of death, diagnosis, or the date of the data collection (31 December 2011), depending on which event that happened first.

Definitions

- Hypertensive disorders were defined as follows: Gestational hypertension as blood pressure $\geq 140/90$ mm Hg after 20 weeks of gestation in at least two readings $\geq 4$ hours apart, pre-eclampsia as a sustained increase in blood pressure to $\geq 140/90$ mm Hg after 20 weeks of gestation combined with proteinuria of at least 1+ or more on a semi-quantitative dipstick ($>300$ mg/24 hours). Hypertension and proteinuria were to be apparent on two different occasions at least 4 hours apart.

- Small for gestational age (SGA) was defined as $<-2$ standard deviations (SDs) below the Swedish growth standard (107).

- Large for gestational age (LGA) was defined as $>2$ SDs above the Swedish growth standard (107).

- Low birth weight (LBW) was defined as birth weight $<2500$ g, very low birth weight (VLBW) was defined as birth weight $<1500$ g and extreme low birth weight (ELBW) was defined as birth weight $<1000$ g.

- Preterm birth (PTB) was defined as birth $<37$ weeks), and very preterm birth (VPTB) as birth $<32$ weeks and extreme preterm birth as birth $<28$ weeks of gestation.

- Perinatal mortality is stillbirths and live born infants with death within the first week of life. In Finland, all stillbirths after 22 completed gestational weeks were included. In Denmark, all stillbirths after 28 completed gestational weeks were included until 2004 and thereafter all stillbirths after 22 completed gestational weeks. In Sweden, all stillbirths after 28 completed gestational weeks were included until June 30, 2008 and thereafter all stillbirths after 22 completed gestational weeks.
Results and comments

Results Paper I

Women who gave birth to girls with Turner syndrome: maternal and neonatal characteristics

Study population (n=494) and control group (n=1,610,754 girls from MBR) are described in figure 9 (study populations and timeline), table 4 (study settings, patients and main outcomes) and the subgroups of Turner karyotype are described in table 3.

The number of girls with TS karyotype born per year is shown in Figure 13.

Figure 13. Number of TS girls born per year since 1973. There is a decline in the end of the study period because of undiagnosed girls.

The median age for a TS diagnosis of any karyotype was 7.9 years (range 0-34 years). The median age was 5.4 years (0-28 years) for TS monosomy, 7.5 years (0-34 years) for TS mosaic, 9.7 years (0-26 years) for TS isochromosome and 9.7 years (0-30 years) for the “other” TS group (p<0.0001).

Among the 494 girls with TS, 11 girls were twins (2.2%), which is similar to the overall twin rate in Sweden during the study period according to the MBR (2.4%). Two twins were the only siblings in all 494 girls. The other nine twins with TS had unaffected co-twins.
Maternal characteristics
Four hundred and ninety-four women were included in the analyses regarding maternal characteristics: four women with TS were excluded (karyotype monosomy (n=1), non-monosomy n=3).

More women above the age of 40 delivered a girl with TS, 3.2% than the 1.8% in the general population (OR 1.83; 95% CI; 1.09-3.08, after adjustment for year of birth). The ORs for TS pregnancies of any karyotype and subgroups in relation to maternal age classes are shown in figure 14-17. Multiple logistic regression analysis with maternal age as the dependent variable using continuous data with one linear and one quadratic term, adjusted for year of birth, is also shown in figure 14-17. A corresponding simultaneous test of the linear and quadratic terms revealed an association between maternal age and TS in the offspring in all karyotypes (p=0.006) mosaic karyotypes (p=0.02) and for isochromosomal karyotype (p=0.03). No association was found between maternal age and monosomy (p=0.16) and “the other” TS karyotype (p=0.62, not shown in fig.).

There was no association between parity or maternal smoking and TS. This applies to all subgroups of TS. Thus, neither parity nor maternal smoking was adjusted for in the multiple logistic regression models.

Figure 14
Results and comments

Figure 15

Figure 16
Results and comments

Figure 17

![Graph showing odds ratio for isochromosome against maternal age.]

**Figure 14-17.** Maternal age and OR for a Turner pregnancy (all karyotypes, Fig. 14, monosomy, Fig. 15, mosaicism, Fig. 16, isochromosome, Fig. 17). Reference group maternal age 30-34 years.

Data on maternal height were not registered in the MBR before 1983; hence this data were missing for 44% of TS mothers and 40% of non-TS mothers. Maternal height was inversely associated with TS pregnancies of any karyotype (p=0.005) using maternal height as continuous data with one linear term. Maternal height was inversely associated with TS pregnancies in the combined group of mosaic, isochromosome and “other” karyotypes (p<0.001), but no association was found between maternal height and risk of having a child with monosomy karyotype (p=0.80). ORs are adjusted for year of birth as well as the multiple logistic regression analyses using maternal height as continuous data with one linear term (Figure 18-20).
Figure 18

Figure 19
Results and comments

Figure 20

![Graph showing maternal height and OR for various Turner pregnancies]

**Figure 18-20.** Maternal height and OR for any karyotype and Turner pregnancy (n=234) (Figure 18). Maternal height and OR for a monosomy Turner pregnancy (n=113) (Figure 19). Maternal height and OR for a mosaic/isochromosome/other Turner pregnancy (n=121) (Figure 20). Women not born in Sweden and women with a diagnosis of TS were excluded. Reference group: maternal height 165-169 cm.

Neonatal characteristics

Four hundred and ninety-four newborns with TS karyotype were included in the study and were compared with 1,610,754 girls from the general population (Figure 21). Preterm birth occurred more often in TS pregnancies than in controls. Late preterm birth (week 32-36) occurred in 10.3% of all TS pregnancies as compared with 4.8% in the general population (AOR 2.23; 95% CI 1.67-2.97). A lower rate of post-term deliveries, 2.8% in the TS group as compared with 8.2% in the general population was seen (AOR 0.32; 95% CI 0.19-0.55). More TS girls were SGA age as compared with non-TS girls in the general population, 17.8% vs. 3.5% (AOR 6.55; 95% CI 5.12-8.38). Fewer TS girls as compared with non-TS girls in the general population were LGA, 0.6% vs. 3.1% (AOR 0.27; 95% 0.09-0.85). Twenty-one percent of girls with TS had a length at birth <-2SD as compared with 3.4% in the general population (AOR 8.69; 95% CI 6.89-10.97). Girls with iso/chromosome and “other” TS karyotypes were the shortest among the TS girls.
Results and comments

Figure 21. Gestational age and size at birth in girls with TS karyotype (n=494) as compared with girls in the general population.

MBR Medical Birth Register, SD standard deviation, TS Turner syndrome

Comments on Paper I

The results show clearly for the first time an association between more mature maternal age and the risk of having a daughter with TS karyotype, for women above the age of 40. Short maternal height as characteristic of women giving birth to a girl with TS karyotype is also a new finding, indicating hereditary factors. There are case reports about women with TS giving birth to TS girls (22, 23, 24). In our study we found four TS karyotype women who gave birth to TS karyotype girls. Since this was a register study, no further information was available on these women. It has been reported that the X-chromosome is most often derived from the mother (21).

The other findings from paper I are that girls with TS were more often SGA and born preterm, confirming previous reports (108-112). The new finding was that girls with isochromosomes and “other” TS karyotypes, rather than girls with monosomy were the shortest among the TS girls. Still the girls with monosomy got their diagnosis earlier, at the age of 5.4 years compared with 9.7 years for all girls with TS karyotype indicative of more external stigmata in these girls.

The decline in postnatal diagnosing of TS karyotype during the later part of the study period is attributable to the fact that a TS diagnosis is set at a median age of 7.9 years. Another explanation might be improved and increased prenatal testing followed by an increased rate of induced abortions. (113-115).
Results and comments

Results Paper II

Obstetric and neonatal outcomes in women with Turner karyotype
Women with Turner karyotype born between 1938 and 1987 (n=115) who gave birth between 1973 and 2007 (n=208 children) were studied. The reference group consisted of 56 000 women from the MBR, matched for year of birth, and their 112 330 singletons. The study population and control group are described in Figure 9 (study populations and timeline), table 3 (study settings, patients and main outcomes), and the subgroups of Turner karyotype are described in table 4.

Maternal characteristics
Maternal characteristics are shown in table 6. Median age at diagnosis in all women with Turner karyotype was 33 years (range 8-65 year). Median age at TS diagnosis differed between the Turner groups (p=0.004), women with monosomy being the youngest and women with mosaic karyotype the oldest. The diagnosis was known in about half of the women at delivery. Women with Turner karyotype were older than the reference population at delivery, median age at first delivery 30 years (range 18-41 years). Women with Turner karyotype were shorter and heavier than the reference population. Smoking habits did not differ.

Obstetric outcome
Pre-existing diseases and complications during pregnancy according to the MBR in women with Turner karyotype were few and did not allow for meaningful statistical analysis in comparison with the general population. The rate of pre-eclampsia in women with Turner karyotype was 6.3% vs. 3.0% in the reference population (OR 1.92; 95% CI 0.94-3.92; P=0.07). Two women had placental abruption. One woman had aortic dissection in her second spontaneous pregnancy. Her diagnosis of TS was set two years after this event.

Neonatal outcome in singletons
Neonatal characteristics in singletons born to women with Turner karyotype 1973-2007 are described in table 7.

<table>
<thead>
<tr>
<th></th>
<th>All women with Turner karyotype</th>
<th>All women with Turner karyotype excluding 45,X/46,XX low-grade mosaicism (&lt;6%)</th>
<th>Medical Birth Register reference group*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=112</td>
<td>n=100</td>
<td>n=56 000</td>
</tr>
<tr>
<td>Age at TS diagnosis,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>years, median (range)</td>
<td>33 (8-65)</td>
<td>33 (8-65)</td>
<td>NA</td>
</tr>
<tr>
<td>Year of first delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1973-1982</td>
<td>17 (15.2)</td>
<td>16 (16.0)</td>
<td>10 875 (19.4)</td>
</tr>
<tr>
<td>1983-1989</td>
<td>15 (13.4)</td>
<td>14 (14.0)</td>
<td>11 453 (20.5)</td>
</tr>
<tr>
<td>1990-1999</td>
<td>41 (36.6)</td>
<td>36 (36.0)</td>
<td>20 634 (36.8)</td>
</tr>
<tr>
<td>2000-2007</td>
<td>39 (34.8)</td>
<td>34 (34.0)</td>
<td>13 038 (23.3)</td>
</tr>
<tr>
<td>Maternal age at first delivery, years, median (range)</td>
<td>30 (18-41)</td>
<td>30 (18-41)</td>
<td>26 (13-48)</td>
</tr>
<tr>
<td>Parity, **</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-p, n</td>
<td>53</td>
<td>47</td>
<td>17 405</td>
</tr>
<tr>
<td>2-p, n</td>
<td>38</td>
<td>34</td>
<td>25 509</td>
</tr>
<tr>
<td>3-p or more, n</td>
<td>21</td>
<td>19</td>
<td>13 086</td>
</tr>
<tr>
<td>Height***, cm, median (range)</td>
<td>161 (140–180)</td>
<td>160 (140–180)</td>
<td>166 (120–190)</td>
</tr>
<tr>
<td>Smoking at first delivery*** (n/N (%))</td>
<td>14/92 (15.2)</td>
<td>10/81 (12.3)</td>
<td>8,035/42,566 (18.9)</td>
</tr>
<tr>
<td>BMI at first delivery, kg/m², median (range)</td>
<td>24.5 (18.0–39.4)</td>
<td>24.5 (18.5–39.4)</td>
<td>23.0 (13.7–61.3)</td>
</tr>
</tbody>
</table>

NA not applicable, MBR medical birth register, TS Turner syndrome, BMI body mass index
* Reference group from MBR (500 controls per TS woman) matched for year of birth
** Seven women with Turner karyotype had deliveries before 1973
*** Height and smoking habits at first antenatal visit registered since 1983 in the MBR
# Data from MBR

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All children born to women with any TS karyotype</th>
<th>All excluding children born by TS women with 45,X/46,XX low-grade mosaicism (&lt; 6%)</th>
<th>MBR reference group*</th>
<th>All children born to women with any TS karyotype vs MBR reference group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=202</td>
<td>n=190</td>
<td>n=330</td>
<td></td>
</tr>
<tr>
<td>Gestational age days, median (range)</td>
<td>273 (168-294)</td>
<td>273 (168-294)</td>
<td>280 (154-315)</td>
<td>-6.4 (-11.1 - -1.8)</td>
</tr>
<tr>
<td>Birth weight g, median (range)</td>
<td>3425 (550 – 5090)</td>
<td>3440 (550-5090)</td>
<td>3540 (366-9905****)</td>
<td>-208 (-333 - -82)</td>
</tr>
<tr>
<td>Low birth weight &lt;2500 g, n (%)</td>
<td>17 (8.5)</td>
<td>15 (8.4)</td>
<td>3865 (3.5)</td>
<td>2.5 (1.4-4.4)</td>
</tr>
<tr>
<td>SD weight, median (range)</td>
<td>-0.1 (-3.8 to 3.0)</td>
<td>-0.1 (-3.8 to 3.0)</td>
<td>-0.1 (-5.0 to 5.0)</td>
<td>-0.1 (-0.3 - 0.1)</td>
</tr>
<tr>
<td>SD length, median (range)</td>
<td>-0.1 (-3.3 to 3.0)</td>
<td>-0.1 (-3.3 to 2.5)</td>
<td>0.1 (-4.9 to 4.9)</td>
<td>-0.1 (-0.2 – 0.1)</td>
</tr>
<tr>
<td>Cesarean section, n (%)</td>
<td>72 (35.6)</td>
<td>68 (37.6)</td>
<td>13209 (11.8)</td>
<td>2.9 (1.9-4.3)</td>
</tr>
<tr>
<td>Apgar score &lt;75, n (%)</td>
<td>4 (2.1)</td>
<td>4 (2.3)</td>
<td>1331 (1.2)</td>
<td>3.1 (0.8-12.5)</td>
</tr>
<tr>
<td>Mortality****, n (%)</td>
<td>3 (1.5)</td>
<td>2 (1.1)</td>
<td>978 (0.9)</td>
<td>1.8 (0.6-5.6)</td>
</tr>
<tr>
<td>Children with any birth defect, n (%)</td>
<td>9 (4.5)</td>
<td>9 (5.0)</td>
<td>4267 (3.8)</td>
<td>1.2 (0.6-2.3)</td>
</tr>
</tbody>
</table>

OR, odds ratio
* Reference group from MBR: the children of 500 controls per TS woman. Women matched on year of birth
** Anova, adjusted for maternal age, robust variance
*** Multiple logistic regression analyses, adjusted for maternal age and parity; robust variance
**** 9905g from MBR
***** Stillbirth or death within 1 year of age
In children of women with Turner karyotype, the median gestational age was shorter and preterm deliveries more common, especially in gestational weeks 32-36. Birth after 42 weeks of gestation was unusual. No difference was found in median SD for weight and length at birth.

The total mortality rate in the children of women with Turner karyotype was 1.5% (3/202) and 0.9% in the control group. Birth defects/chromosomal aberrations occurred in 9 children of women with Turner karyotype (4.5%) and in 4267 (3.8%) children of mothers in the reference group. Two of the birth defects were chromosomal aberrations and at least two were minor (hip dislocation). None of the 9 mothers had a monosomy karyotype.

There was no significant difference between the maternal Turner karyotypes regarding any investigated neonatal outcome.

**Neonatal outcomes in twin pregnancies**

Neonatal outcomes in twin pregnancies were complicated by two preterm deliveries in gestational weeks 34 and 30. One of these twins had an aortic coarctation. Two twin pregnancies took place after oocyte donation. For the third pregnancy no information on mode of conception was available.

**Comments on Paper II**

This study is one of the largest and one of the first controlled registry studies on obstetric and neonatal outcomes in women with Turner karyotype.

TS pregnancies are at high risk, as described in previous studies, owing to the risk of aortic dissection, but the increased risk of hypertensive disorders in TS pregnancies could only be seen as a trend towards more pre-eclampsia. The rate of pre-eclampsia was doubled but not statistically significant, probably owing to small sample size. The neonatal outcome after deliveries in women with Turner karyotype was reassuring.

This good outcome may be explained by a healthier cohort of women with Turner karyotype. Few women had a monosomy karyotype, in which morbidity is increased. The age at diagnosis of Turner karyotype was high (median 33 years), also indicating a healthier cohort of women, with few stigmata.
Results Paper III

Obstetric and neonatal outcomes after oocyte donation in 106 women with Turner syndrome: a Nordic cohort study

Women with Turner syndrome (n=106) who gave birth after OD in Finland, Denmark and Sweden between 1992 and 2011 (n=131 children) were studied. Study population is described in figure 9 (study populations and timeline), table 3 (study settings, patients and main outcomes) and the subgroups of Turner karyotype are described in table 4. Norway was not included since OD is prohibited, and Iceland did not answer the invitation to participate.

Maternal background
Maternal characteristics are described in table 8.

Cardiovascular evaluation before pregnancy
Ten women (9.4%) had a known cardiac defect before pregnancy, and in four of these women the defect had been surgically corrected (aortic coarctation [n=2], aortic stenosis [n=2]). Pre-pregnancy cardiovascular examination by a cardiologist had been performed in 73 women (63.5%) and in 56 women (48.7%) less than two years before OD treatment. Except for the women with known cardiac defects, all pre-pregnancy cardiac examinations were normal (Table 8).

Cardiovascular evaluation during pregnancy
Echocardiography or magnetic resonance imaging (MRI) was performed in a total of 35 pregnancies (28.7%), in 5/10 with a known cardiac defect, table 8. In one woman with a previously normal cardiovascular examination, mild left ventricular dilatation with regurgitation was found in gestational week 21. Another woman had an emergency computed tomography (CT) in late pregnancy. She had developed severe pre-eclampsia and had chest pain. The CT was considered normal but later appeared to have been misdiagnosed when an aortic dissection was diagnosed after delivery. After this paper was accepted for publication, further information was obtained for one woman who had an aortic dilation of 40 mm before and during pregnancy. She was checked several times during pregnancy, had beta-blocker-prophylaxis, and the pregnancy was without complications. She was delivered by CS in gestational week 41 after failed induction of labour.

All other women (27/32) with normal cardiovascular examinations before pregnancy also had normal cardiovascular evaluations during pregnancy.
Table 8. Background characteristics\(^a\) in women with TS who delivered after OD in Sweden separately and in the Nordic countries.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Women with TS, n</td>
<td>32</td>
<td>106</td>
</tr>
<tr>
<td>Karyotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monosomy, n (%)</td>
<td>14/30 (46.7)</td>
<td>44/100 (44.0)</td>
</tr>
<tr>
<td>Mosaic, n (%)</td>
<td>3/30 (10.0)</td>
<td>16/100 (16.0)</td>
</tr>
<tr>
<td>Other TS karyotypes(^b), n (%)</td>
<td>13/30 (43.3)</td>
<td>40/100 (40.0)</td>
</tr>
<tr>
<td>Age at diagnosis, median (range)(^a)</td>
<td>12.0 (0-22)</td>
<td>13.0 (0-42)</td>
</tr>
<tr>
<td>Height, cm median (range)</td>
<td>156 (140-164)</td>
<td>154 (138-170)</td>
</tr>
<tr>
<td>Unknown, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI(^a), median (range)</td>
<td>25 (19-33)</td>
<td>24 (18-42)</td>
</tr>
<tr>
<td>Smoking, yes, n (%)(^c)</td>
<td>1/32 (3.1)</td>
<td>14/100 (14.0)</td>
</tr>
<tr>
<td>Chronic hypertension(^d), n (%)</td>
<td>1/32 (3.1)</td>
<td>4/106 (3.8)</td>
</tr>
<tr>
<td>Diabetes mellitus(^d), n (%)</td>
<td>1/32 (3.1)</td>
<td>4/106 (3.8)</td>
</tr>
<tr>
<td>Thyroid disease(^d), n (%)</td>
<td>14/32 (43.8)</td>
<td>23(^e)/106 (21.7)</td>
</tr>
<tr>
<td>Renal disease(^d), n (%)</td>
<td>5/32 (15.6)</td>
<td>6(^f)/106 (1.9)</td>
</tr>
<tr>
<td>Hepatic disease(^d), n (%)</td>
<td>1/32 (3.1)</td>
<td>2(^g)/106 (1.9)</td>
</tr>
<tr>
<td>Congenital heart defects, n (%)</td>
<td>2/32 (6.3)</td>
<td>10/106(^h) (9.4)</td>
</tr>
<tr>
<td>Cardiovascular examination before pregnancy(^i), n (%)</td>
<td>31/31(100)</td>
<td>73/115 (63.5)</td>
</tr>
<tr>
<td>Cardiovascular examination &lt;2 years before pregnancy(^j), n (%)</td>
<td>22/31 (71.0)</td>
<td>56/115 (48.7)</td>
</tr>
<tr>
<td>Cardiovascular examination with ECG/MRI during pregnancy(^k), n (%)</td>
<td>17/26 (65.4)</td>
<td>35/122 (28.7)</td>
</tr>
<tr>
<td>Age of mother at first OD delivery, median (range)</td>
<td>31.5 (23-40)</td>
<td>32.0 (22-46)</td>
</tr>
<tr>
<td>Nulliparity at first OD delivery, n (%)</td>
<td>32/32 (100)</td>
<td>105/106 (99.1)</td>
</tr>
<tr>
<td>Women with 1 OD delivery, n (%)</td>
<td>29/32 (90.6)</td>
<td>90/106 (84.9)</td>
</tr>
</tbody>
</table>

BMI body mass index, ECG echocardiography, MRI magnetic resonance imaging
\(^a\) there are missing data on some outcomes
\(^b\) other=45,X/46X, i(X) 46X,i(X) 45,X/46,XY 45,X/46,XY/47,XXX 45,X/47,XXX 45,X/46,XX/47,XXX/48,XXXX 45,X/46der(X) (including ring chromosomes, deletions, inversions and translocations)
\(^c\) at first antenatal appointment at first OD delivery
\(^d\) a woman can have more than one disease
\(^e\) hypothyroidism (n=21), hyperthyroidism (n=2)
\(^f\) bilateral double renal pelvis (n=1), nephrotic syndrome (n=1), renal transplant due to haemolytic uremic syndrome (n=1), unilateral congenital renal atresia (n=1)
\(^g\) elevated liver enzymes
\(^h\) bicuspid aortic valve (n=1), aortic coarctation (n=1), small ventricular septal defect (n=1), aortic regurgitation (n=1), aortic coarctation (n=1), aortic and tricuspid regurgitation (n=1), aortic stenosis (n=1), hereditary cardiac valve disease (n=1) aortic stenosis with mechanical heart valve (n=1), small ventricular septal defect (n=1)
\(^i\) per delivery
Results and comments

Obstetric outcomes

Obstetric outcomes are presented in figure 22. Multiple birth rate was 7.4%. “Vanishing twin” of one twin occurred in two of the twin pregnancies, and two foetal reductions (from twins to singletons) were performed. Of all pregnancies, 35.0% (41/117) were associated with a hypertensive disorder including pre-eclampsia in 20.5% (24/117). CS was performed in 82.0% (100/122) of all deliveries.

Potentially life-threatening complications occurred in 3.3% (4/122) pregnancies.

One woman with severe bleeding was treated with high dose anticoagulant therapy owing to a mechanical heart valve. At the beginning of OD treatment, she had a BMI of 31 and hypothyroidism, karyotype 45,X/46,XY/47,XXX. She developed severe pre-eclampsia with HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome and was delivered by CS in gestational week 29. The OD treatment in 2006 was her eighth attempt to achieve a pregnancy. Both mother and child recovered.

One 28-year-old woman with a TS mosaicism had an aortic dissection in 2009. She had had several OD treatments before she became pregnant. She had a BMI of 28 and substituted hypothyroidism, but was otherwise healthy with a normal cardiovascular examination before pregnancy. She developed severe pre-eclampsia in gestational week 38 and a CT was performed a few days before delivery owing to chest pain, but without confirming an aortic dissection. The diagnosis of aortic dissection was made 20 days after delivery, when she presented with acute symptoms of severe chest pain and dyspnoea. A new CT showed aortic dissection. The first CT was re-evaluated and it was confirmed that the aortic dissection could have been diagnosed at the first CT scan. She was treated conservatively and surgical correction was successfully performed 1.5 years later.

One 42-year-old woman with a TS mosaicism was diagnosed with heart regurgitation and left ventricular dilatation in gestational week 21 in 2008. She had hypothyroidism and chronic hypertension treated with antihypertensive drugs before pregnancy. Cardiovascular examination before pregnancy was normal. No further complications occurred and she was delivered by elective CS at term, without any further complications.

One 32-year-old woman developed heart failure, albeit mild, diagnosed in gestational week 28. She had normal pre-pregnancy cardiac evaluation, but chronic hypertension and hypothyroidism. Her karyotype was mosaic. She was treated with anti-hypertensive medication during pregnancy and was delivered by elective CS at term, without any further complications.
Renal diseases occurred in 5 women, all from Sweden (5/32, 16%). Pregnancies were in two cases uncomplicated, in spite of the fact that one of them had diabetes type 2 and a history of a small cerebral bleeding six years ahead of pregnancy. Both were delivered by CS. In the other three the first was complicated by severe pre-eclampsia. She was delivered vaginally but had a big bleeding and blood transfusions because of placenta retention. The second woman had been kidney transplanted five years ahead of pregnancy owing to severe infection, and developed hydronephrosis and signs of reduced kidney function. Induction of labour started, in gestational week 36 but since there was no progress she was delivered by CS with no complication. The third woman had a nephrotic syndrome, B12 deficiency, slight aortic insufficiency and stable aortic dilation on 40-41 mm. Beta-blockade prophylaxis was used from gestational week 25 and the pregnancy went uneventful. She was delivered by CS after failed induction in gestational week 41. She was followed thoroughly up by cardiologists during the pregnancy.

All children born were healthy.

No thromboembolic complications or deaths were reported during pregnancy, delivery or before discharge from the maternity ward.

Median follow-up time was four years (4 months to 19 years) after last delivery. One woman died nine years after delivery, cause of death is unknown.

![Figure 22. Pregnancy complications in singletons (n=113) and twins (n=9 pregnancies) in women with TS and OD.](image-url)
Results and comments

Neonatal outcomes
Neonatal outcomes are presented in figure 23. PTB (<37 weeks) occurred in 8.0% (9/113) of singletons and in 66.7% (6/9) of twin pregnancies. LBW (<2500g) occurred in 8.8 % (10/113) of singletons and 72.2% (13/18) of twins. The perinatal mortality was 2.3% (3/131). One unexplained stillbirth occurred in gestational week 42 and one twin pair were born SGA in gestational week 25 and died shortly after birth owing to immaturity. Singletons of primiparous women with 45,X monosomy were compared with those of primiparous women with a mosaic or other TS karyotype and there were no differences in median gestational age (p=0.63), median birth weight (p=0.81) or median percentage of birth deviation (p=1.0).

![Figure 23. Neonatal outcomes in singletons (n=113) and twins (n=18) in women with TS and OD.](image)

SGA small for gestational age, LGA large for gestational age, PNM perinatal mortality

Comments on Paper III
To my knowledge this is the largest study on deliveries after OD in women with TS. The study period was 20 years and all, but four identified Turner oocyte recipients but four were included in Sweden, Finland and Denmark. Despite some differences in maternal characteristics (smoking) and in embryo transfer strategy, outcomes were similar in the different countries. Few data were missing, especially for neonatal outcomes. The study confirms that pregnancies in women with TS are high-risk, because of complications such as hypertensive disorders, placental complications and aortic dissection (one woman). Four women in this study had life-threatening complications.
The woman with aortic dissection was misdiagnosed during pregnancy, illustrating the difficulties in diagnosing correctly and the importance of centralized evaluation of women with TS, as studied by Boissonnas et al., 2009 (116). According to American guidelines from 2012 (102), at least 10 of the women in this study would probably be denied OD today, owing to cardiovascular malformations. The knowledge about risks in women with TS has increased in recent years, which explains why pre-pregnancy cardiac evaluations were not performed prior to 2000.

Neonatal outcome for singletons was reassuring as compared with other children born after OD and IVF (117-119), and better than previously reported in women with TS (37, 38, 88). Twin pregnancies had more complications than singleton pregnancies, strengthening the advice to avoid double embryo transfer in women with TS.

One limitation of the study was the absence of a control group. Data were collected with help from IVF clinics and with written informed consent from all participating women. The optimal design would have been to have all other OD treated women as controls. It was not considered possible to obtain these data from all IVF clinics in the Nordic countries.

Furthermore, data on unsuccessful cycles for the complete Nordic cohort of women with TS were not available. In recent years in the Nordic countries, the live birth rate for women with TS and OD was reported from the largest clinic in Finland (1999-2008) as 33%, in Denmark (1995-2011) 30% and in one of the largest clinics in Sweden (2003-2011) 33%. This rate is comparable to other Nordic results after OD in the general population (Finland 25.2% (2010), Sweden 33.5% (2009) and Denmark 24.2% (2007-2009) (Personal communications 2013: V Söderström-Anttila (Finland), A Loft (Denmark), C Bergh (Sweden)).
Results Paper IV

Morbidity and mortality after childbirth in women with Turner karyotype

Women with Turner karyotype born between 1957 and 1987 (n=124) who gave birth between 1973 and 2010 were studied. Study population and control group are described in figure 9 (study populations and timeline), table 3 (study settings, patients and main outcomes) and the subgroups of Turner karyotype are described in table 4.

Background characteristics

Median age at diagnosis was 30.6 years for women with Turner karyotype and childbirth and 12.0 years for women with Turner karyotype and no childbirth. Median age at follow-up on 31 December 2011 was 42 years (range 24 to 54 years) for women with Turner karyotype with childbirth and controls from MBR and 33 years (range 24 to 54) for women with Turner karyotype without childbirth.

Median age at first delivery was 31 years for women with Turner karyotype and the MBR control group.

Mortality

No mortality was found in women with Turner karyotype and childbirth. There were 14/378 (3.7%) deaths in women with Turner karyotype without childbirth and 9/1,230 (0.7%) in the MBR control group. Causes of death in women with Turner karyotype were in 7/14 (50%) owing to diseases of the circulatory system. Five (1.3%) of the women with Turner karyotype died from aortic rupture (Table 11 aortic aneurysm). Two were monosomy 45,X and 3 belonged to the subgroup of other Turner karyotypes.

Morbidity

Morbidity by age at first diagnosis and morbidity in relation to pregnancy were registered. Data were obtained from the NPR and CDR.

Diseases of the circulatory system and congenital heart defects

In general, women with Turner karyotype had higher rates of diseases of the circulatory system than controls from the MBR 11.0% vs 3.9% (HR 3.31; 95% CI 2.18-5.02). Statistically significant for women under the age of 40 (HR 4.59; 2.75-7.66) but not for older women. The higher rates were seen irrespective of childbirth in women with Turner karyotype. The most common diagnoses in women with Turner karyotype were valvular disease 12/502 (2.4%) and aortic aneurysm 11/502 (2.2%) under the age of 40. Aortic aneurysm was not registered in Turner women older than 40 years or in the control group.

Two women with Turner karyotype and childbirth had an aortic dissection diagnosed shortly after and during pregnancy at 30 and 37 years of age. One had 45,X monosomy and one had 45,X/46XY karyotype. Both also had cardiac defects diagnosed during the same hospitalization period, after dissection (one had aortic coarctation and stenosis and one had...
### Table 11. Aortic aneurysm in women with Turner karyotype born after 1957 and diagnosed after 1987.

<table>
<thead>
<tr>
<th>ICD code</th>
<th>Year of birth</th>
<th>Age at diagnosis of aortic aneurysm</th>
<th>Year of diagnosis</th>
<th>Karyo-type</th>
<th>Year of diagnosis Turner karyotype</th>
<th>Comments</th>
<th>D=dead</th>
<th>A=alive</th>
</tr>
</thead>
<tbody>
<tr>
<td>I711</td>
<td>1971</td>
<td>28</td>
<td>1999</td>
<td>45,X</td>
<td>25</td>
<td></td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>I718</td>
<td>1969</td>
<td>37</td>
<td>2006</td>
<td>other</td>
<td>32</td>
<td>Aortic coarctation</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>I71</td>
<td>1977</td>
<td>29</td>
<td>2006</td>
<td>other</td>
<td>13</td>
<td>Epilepsy</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>I719</td>
<td>1981</td>
<td>25</td>
<td>2006</td>
<td>other</td>
<td>4</td>
<td>Multiple diseases, 58 hospitalizations 1988-2006*</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>I71</td>
<td>1979</td>
<td>30</td>
<td>2009</td>
<td>45,X</td>
<td>13</td>
<td>Aortic dilation 2005</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>I710</td>
<td>1977</td>
<td>26</td>
<td>2003</td>
<td>45,X</td>
<td>0</td>
<td>Aortic coarctation**</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>I712</td>
<td>1976</td>
<td>30</td>
<td>2006</td>
<td>45,X</td>
<td>0</td>
<td>Dilated cardiomyopathy, infection and endocarditis</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>I710</td>
<td>1975</td>
<td>34</td>
<td>2009</td>
<td>45,X</td>
<td>11</td>
<td></td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>I772**</td>
<td>1988</td>
<td>23</td>
<td>2011</td>
<td>45,X</td>
<td>0</td>
<td>0. Same year, left cardiac insufficiency</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td><strong>Pregnant women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I710</td>
<td>1961</td>
<td>37</td>
<td>1998</td>
<td>other</td>
<td>39</td>
<td>Parity 2 Aortic coarctation*** Pheochromocytom***</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>I710</td>
<td>1981</td>
<td>28</td>
<td>2009</td>
<td>45X/46,XX</td>
<td>10</td>
<td>Parity 1 OD Preeclampsia Bicuspid valves***</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>I712</td>
<td>1980</td>
<td>30</td>
<td>2010</td>
<td>45,X</td>
<td>0</td>
<td>Parity 1 OD Nephrotic syndrome, B12 deficiency, endocarditis (streptococcus) Aortic dilation 41mm and small VSD</td>
<td>A</td>
<td></td>
</tr>
</tbody>
</table>

| all women  | median 29 years | median 11 years | 5 dead | 7 alive |

** born 1988 and therefore not included in Paper IV
*** diagnosis was set after dissection
unspecified septal defect). They were delivered with healthy babies by CS in gestational weeks 32 and 38. There was also one woman with an aortic dilation during pregnancy, without dissection, also delivered by CS, one week post-term. This dilation was known before pregnancy and did not change during pregnancy.

In addition to the 5 women who died, 4 women with Turner karyotype and no childbirth had aortic aneurysm, see table 11 aortic aneurysm.

Risk factors seen in patients with dilation and dissection were monosomy (7/12), cardiac defect (7/12), and pregnancy (3/12). The incidence of more exact phenotype and diseases, like hypertension could not be obtained from the registers used, while outpatient data is not registered in these.

A cardiac malformation was registered in 23/502 (4.6%) (2.6% coarctation of aortae and 2.0% bicuspid valves) of all women with Turner karyotype under the age of 40 and predominantly among women without childbirth. In the MBR control group 3/1, 1230 (0.2%) had a cardiac malformation.

Diseases of the circulatory system were elevated overall for women with Turner karyotype and childbirth as compared with the MBR control group (HR 2.82; 95% CI 1.53-5.21), before first pregnancy, during any pregnancy and within one year after first delivery (HR 3.83; 95% CI 1.02-14.43 and HR 5.78; 95% CI 1.94-17.24) but not one or more years after delivery (HR 1.91; 95% CI 0.74-4.96).

**Endocrine diseases**

Women with Turner karyotype (with and without childbirth) had higher rates of endocrine, metabolic and nutritional diseases than the MBR control group (21.5% versus 5.6%, HR 2.73; 95% CI 1.86-4.01), mainly thyroid diseases (8.9% versus 2.3%, HR 3.22; 95% CI 1.88-5.34).

Women with Turner karyotype with and without childbirth had similar rates of endocrine, metabolic and nutritional diseases.

**Gastrointestinal and other diseases**

Women with Turner karyotype had similar rates of gastrointestinal diseases as women in the MBR control group.
**Results and comments**

**Cancer**

Malignant tumours occurred in 3/124 (2.4%) of the women with Turner karyotype and childbirth in 11/378 (2.9%) of the women with Turner karyotype and no childbirth and in 2.0% in the MBR control group. Breast cancer was only seen in one woman (0.2%) with Turner karyotype as compared with 0.7% in the control group. Ovarian cancer was found in two women with Turner karyotype.

**Comments Paper IV**

This study is the first controlled registry study on morbidity and mortality after pregnancy in women with Turner karyotype.

There are very few studies concerning health effects of pregnancies and childbirths in women with TS. There has been a tendency to publish catastrophic case reports, leading to a restrictive attitude to women with TS desiring OD. The mechanism of aortic dissection in women with TS is not fully known, which explains why all women with TS have been considered to be at risk.

The overall morbidity and mortality are increased in general in women with Turner karyotype irrespective of childbirth. These women are more frequently affected by diseases and at younger ages, mostly by cardiovascular diseases and endocrine diseases. Pregnancy and childbirth may enhance the risk of aortic dissection due to increased risk for hypertensive disorders, especially in OD pregnancies (see Papers II and III). Still, the risk after childbirth does not seem to be elevated.

The risk of aortic dissection is a life-threatening risk in Turner women and difficult to predict. It even hits at young ages. In the summary from Swedish cases with aortic aneurysms, the risk for dilation/dissection are in agreement with previous reports and associated with monosomy, cardiac defects and pregnancy, although it does occur unpredictably.

The importance of good follow-up of women with Turner karyotype cannot be over-emphasised.
**Discussion**

**Maternal characteristics of women giving birth to a girl with Turner karyotype**

Paper I is the first population-based controlled study that clearly identifies advanced maternal age as a characteristic of women giving birth to a girl with TS. Risk factors for giving birth to a girl with TS have been conflicting in previous reports, indicating both high and low maternal ages as factors increasing the incidence of TS (25, 26, 120, 121). Other chromosomal aberrations, such as trisomy 13, 18 and 21 are related to maternal age. Recent studies have shown that oocyte quality could have age related dysfunctions, especially disturbances of the mitochondrial function and consequent loss of the energy essential for proper oocyte function (122) which may explain the maternal age effect. The mitochondrial genome is inherited exclusively from the mother (123). In Forabosco’s and collaborators study from 2009 an increased incidence of TS mosaic foetuses was seen in women above 35 years of age (121). Prenatal screening for foetal and chromosomal abnormalities is common among women above 35 years of age. An increase in induced abortions in Sweden when chromosomal abnormalities are found can be seen (124). Many women and couples may choose to abort a foetus with a Turner karyotype, even when there are no signs of other abnormalities on ultrasonography. Still, the results of our study showed that advanced maternal age was a risk factor for giving birth to a girl with TS.

The short height of the mother was also a characteristic of the mother of a Turner girl with any karyotype except monosomy, 45,X karyotype. This finding gives us reason to speculate on the possibilities of an inherited chromosomal defect, transmitted from mother to daughter as seen in four women who gave birth to girls with TS. The characteristics of the newborn girls with Turner karyotype confirmed previous reports (109, 110, 112) but now also in relation to the general population. One interesting finding was that fewer neonates with 45,X monosomy were less than -2SD in length at birth as compared with other karyotypes. Later in life, these girls and women are the shortest and have more stigmata, which is confirmed by the younger age at diagnosis (19). More research is needed to explain these findings. It is important to consider TS in a newborn girl with short length, less than -2SD, even when the mother is short.

**Reproduction in women with Turner karyotype**

Infertility seems to be one of the greatest problems among TS women. Since ART and OD have been possible since the 1980s, women with TS have had the possibility to become
Discussion

pregnant and have children. The relevant legislation was adopted in 2003 in Sweden, before which Swedish women had to go abroad for this treatment.

This thesis reports on women with Turner karyotype beginning in the early 1970s and who gave birth. Until 1983, when the first OD was reported, these pregnancies are likely to have been spontaneous. Between 1983 and 2003 there may be a mixture of spontaneous pregnancies and pregnancies after OD or IVF. After 2003 more of the pregnancies are likely to be ODs. Only in paper III was it possible to be certain of the mode of conception. These studies are some of the largest on women with Turner karyotype and childbirth.

Maternal characteristics and pre-existing morbidity in women with Turner karyotype and childbirth

In Paper II, pre-existing diseases were only registered in a few women, indicating a healthier population with Turner karyotype. This can be supported by that the Turner diagnosis was unknown for more than 50% of the mothers and they had been diagnosed much later than expected for a Turner cohort. Only 9% had 45,X monosomy karyotype, which is much less than generally found among women with TS (19, 32). These women were also taller than women with TS in general, although they were shorter than the reference group. It may be presumed that the most common indication for chromosomal analysis in these women was infertility, recurrent abortions or premature ovarian failure rather than typical stigmata. Among women with premature ovarian failure, low-grade mosaicism 45,X/46,XX or structural defect on the X-chromosome (deletion) occurs. Loss of one X-chromosome is also seen in normal ageing (31). The diagnosis of TS should not be set if there are no other stigmata of TS in these women. In Paper IV, subgroup analyses were performed excluding the low-grade mosaic women. This did not change any of the main results. All women in the Swedish Turner Register had the diagnosis of TS, although the phenotype was not known to us.

Women with TS in the Nordic study on OD pregnancies in Paper III were younger at diagnosis than the women in paper II (13 vs. 33 years). They all had a known TS diagnosis with both karyotype and presumably phenotype in agreement with the syndrome before pregnancy, and more women had a monosomy karyotype (44% as compared with 9% in Paper II). Thyroid disease was seen in 22% in the whole Nordic group and among Swedish women in the same study, thyroid disease was seen in over 40% of pregnant women. Testing for thyroid disease occurred frequently in this group of TS women both because applying for OD and because of the TS diagnosis itself. The incidence of endocrine diseases was clearly elevated in Paper IV as well, owing to thyroid diseases. This finding confirms a previous
Report from Sweden (48) and a report from USA indicating 37% autoimmune thyroiditis in TS women vs. 15% in karyotypically normal women with premature ovarian failure (54). This higher prevalence of autoimmune disorders in women with TS has been studied, and X-linked mechanisms might explain the susceptibility to autoimmune disorders (125).

Renal disease, chronic hypertension, diabetes mellitus and hepatic disease among the women with TS and OD (paper III) were in agreement with previous reports on morbidity among Turner women, but still not as common as could have been expected (43, 55, 126). Pre-existing diseases complicate the obstetric outcome in women with TS like in all women and the obstetric outcomes after OD are even more complicated than pregnancies after spontaneous pregnancies, in general. Although the women with TS in the Nordic study were affected by more diseases than the women in Paper II, the women treated with OD in Paper III were healthier than expected in comparison with other studies on morbidity in women with TS (126).

In recent years and especially since 2003, women with severe cardiac defects may have been advised to avoid pregnancy, and to some extent this could explain the “healthier” results. Still, TS women with both severe renal malformations and cardiac defects were treated with OD, and this is not recommended in the recent international guidelines (102, 103).

Diseases of the circulatory system and endocrine diseases occurred more often in women with Turner karyotype (with or without childbirth) before the age of 40 than in the MBR control group (Paper IV). Thus, women with TS are struck by severe cardiovascular diseases even at young ages. Why this is so requires further research.

The differences in study cohorts and study design with additional data collected from more registries in paper IV explain much of the differences in morbidity found in these studies.

**Preconceptional evaluation**

Cardiac evaluation is recommended today for all Turner women applying for OD treatment according to the national and the international guidelines (101-104, 127) and should also be recommended for women trying to achieve spontaneous pregnancy. In our Nordic study on OD, pre-pregnancy evaluation by a cardiologist (MRI or echocardiography) was performed in 64%. In 49% the evaluation was performed within two years ahead of the OD treatment. There was an increase in cardiac evaluations during the study period. This was probably because of increased knowledge about the high risk for aortic dissection in women with TS (36, 127).
One case of aortic dissection occurred even after a normal pre-pregnancy cardiac screening. After the event she was diagnosed with bicuspid aortic valve. It is important that the radiologist/cardiologist examining a Turner patient is aware of the TS diagnosis and the specific spectra of abnormalities. If the previous examination was done long ago or performed by a radiologist/cardiologist not familiar with TS, a cardiac re-evaluation is necessary (116).

Ten women (9%) in paper III, had known cardiac defects and this incidence would most probably have been higher if all women had been offered thorough cardiac examinations.

In addition to cardiac evaluation before considering pregnancy or OD, it is also recommended to examine kidney and thyroid function, glucose and liver variables. The substantial increase of related diseases in TS may induce pregnancy complications such as hypertensive disorders.

**Obstetric outcomes in women with Turner karyotype**

In the study of 115 women with Turner karyotype (Paper II) who gave birth between 1973 and 2007, it was hypothesized that, the overall morbidity including hypertensive disorders during pregnancy should be elevated. This was not confirmed, except for one woman with an aortic dissection and a trend towards more TS women having pre-eclampsia during their first pregnancy as compared with the reference group (6.3% vs. 3.0%).

Fewer OD pregnancies and a healthier group of women with Turner karyotype are the most probable explanation of the finding of less hypertensive disorders than expected. OD is known to cause high rates of gestational hypertension and pre-eclampsia in non TS women (27-31%), as in women with TS (38-70%) (38, 88, 93, 97, 98, 128). The high incidence of pre-eclampsia in OD pregnancies could be caused by a high incidence of placental pathology, altered immune response and a high degree of antigenic dissimilarity (94, 129).

As compared with the results in Paper II, a higher rate of hypertensive disorders, 35%, was found in pregnancies after OD (Paper III). All four women with life-threatening complications had hypertension during pregnancy. Two of them had chronic hypertension and two had severe pre-eclampsia.

In Paper IV, three (2.4%) women with TS had aortic complications during pregnancy or within one year after delivery (two had dissections and one had dilation), as compared with the rate of 14.5/1 000 000 seen during pregnancy in Sweden 1987 to 2007 (91). The cardiovascular strain of pregnancy and risk of hypertensive disorders contribute to an extra risk for dissection in women with TS as in women with other collagen diseases as Marfan’s and Ehlers-Danlos’ syndrome (130).
Aortic dissection is unpredictable and strict control of blood pressure is of utmost importance. Other potentially life-threatening complications than aortic dissections occurred in three women, in one bleeding due to placenta accreta, in one heart failure, and in one pregnant woman with a mechanical heart valve after surgery for aortic stenosis earlier in life, thus 5/6 were cardiovascular diseases. However, the previously found maternal mortality rate of approximately 2% in other studies was not confirmed (36, 38).

Placental complications were best documented in our Nordic study. The risk of bleeding both in the first and third trimesters was previously reported as a complication seen in OD pregnancies (131). In our study, 5 (4%) cases of placental complications occurred and severe bleeding was seen more often than expected in comparison with deliveries in the general population (7% vs. 3-5%). It was not possible to analyze data on first trimester hemorrhaging or miscarriages. The reason for the increased rates of hemorrhaging and placental complications in OD pregnancies is unclear but placental implantation abnormalities have been discussed (94).

CS is the dominant mode of delivery in women with TS and OD (38, 76, 88, 89). The most common reasons are the small stature of the women and feto-pelvic disproportion. When induction of labor was performed it often failed, owing to slow or no progress in labor. In our Nordic study 83% of women with singletons were delivered by CS and these women were shorter than the women who had spontaneous vaginal delivery. There are only case reports on women with TS and mode of delivery after spontaneous conception. In Paper II, including both OD and spontaneous pregnancies, the rate of CS was lower, 36%, but still higher than in the reference population. Accordingly, there is reason to believe that vaginal deliveries occur more often in spontaneous than in OD pregnancies.

**Neonatal outcomes in women with Turner karyotype**

In Paper II neonatal outcomes in women with Turner karyotype were reassuring. More infants were born late preterm but with similar size at birth as neonates in the general population. Previous studies, often case reports, have reported high incidences of stillbirths and malformations in TS children (23).

In the Nordic cohort study (Paper III) the neonatal findings in singletons were in parity with the findings in Paper II. In IVF and OD pregnancies in general, the rate of preterm births and SGA are elevated (117-119). The present findings were better than those previously reported in women with TS (37, 38, 88). The reason for these better neonatal outcomes in the Nordic study is not clear, but may be an effect of patient selection and embryo transfer strategy. A clear difference was seen in twins as compared with singletons. In general, twin pregnancies
are more complicated, with increased risk of gestational hypertension, pre-eclampsia, placental complications, SGA and preterm birth. In the Nordic study, outcomes of twin pregnancies were poor, with a high incidence of preterm birth and one extreme preterm birth of a pair of twins, both of whom died within a couple of days. Only 5/18 twins had a birth weight above 2500g. These findings strengthen the recommendation of single embryo transfer in all ODs, and particularly in women with TS.

In our studies it was not possible to differentiate between outcomes from spontaneous pregnancies and OD pregnancies. However, no difference in outcome depending on karyotype was documented.

**Follow-up after pregnancy in women with Turner karyotype**

Cardiovascular and endocrine diseases in women with Turner karyotype were elevated before, during and within one year after pregnancy but not more than one year after delivery, indicating the pregnancy period as a risk factor, but not a long lasting one. However, today, there is much evidence that hypertensive disorders during pregnancy is associated with increased risk of cardiovascular diseases later in life (132). The median follow-up time in our study of ten years after delivery may be too short to see an effect on cardiovascular diseases.

The rate of cancer among women with Turner karyotype, was not found to be elevated in this study. Some cancer forms have been overrepresented in previous studies (53). Larger cohorts of women with TS are needed to draw any more specific conclusions.

*Mortality in women with Turner karyotype*

No mortality in women with Turner karyotype was registered in relation to pregnancy in the present studies.

The overall mortality in women with TS without childbirth was elevated fivefold in comparison with controls, 3.7% as compared to 0.7%, and 7/14 women died from diseases of the cardiovascular system, five from aortic dissection at a young age, median 29 years (table 11 aortic aneurysm in results). This is in line with previous reports (32, 39, 52, 133).

*In conclusion*, the most important evaluation in women with TS is the cardiac examination, familiar with TS. Women with aortic coarctation, aortic dilation and bicuspid aortic valves should have close surveillance. Pregnancies in women with Turner karyotype are associated with a substantial risk of hypertensive disorders and placental complications. In women with TS and cardiovascular morbidity pregnancy could result in severe morbidity and mortality during pregnancy. They should be informed about the risks and be recommended to avoid pregnancy. Careful evaluation performed by a cardiologist before and during pregnancy is mandatory.
Strengths and limitations

Various validated national health registers enabled us to study a cohort of women with TS and with a relatively rare event as childbirth.

**Internal validity, bias and confounders**

The risk of selection bias decreases when using register-based data rather than hospital-based data. The present studies used data from the Swedish Genetic Turner Registry and the MBR. There is most likely no selection of cases reported with a diagnosis of TS to the Swedish Genetic Turner Registry or of births to the MBR. However, the number of girls and women with TS included in the Swedish Genetic Turner Registry is lower than expected according to prevalence data in the literature (32, 35). Furthermore, women with TS and childbirth probably represent a selection of a healthier cohort of women with TS as indicated by maternal characteristics and age at diagnosis and that the Turner diagnosis was not known in more than 50% of the women in Paper II.

There may be a risk of information bias using the NPR as a source of diagnoses. The existence of one diagnosis affects the likelihood of another diagnosis to being given. Women with TS are more often than women from the general population admitted to hospitals or other health care services, because they already suffer from one disease. Furthermore, outpatient data were not available for Papers I, II, IV, but this was similar for cases and controls.

The disadvantages with registers are that it is not possible to check original data as the registers are anonymized.

In all observational studies there is a risk of uncontrolled or residual confounders that could have influenced the results. One example in this thesis is the lack of information of paternal height and age in paper I.

**External validity**

In paper III, data were obtained from three different countries with similar results and there was a high participation rate supporting generalization of the results to other comparable populations.

**Precision/chance**

One limitation concerning all the studies in this thesis is that for rare events large series are needed. Owing to the different starting dates of the registers, it was difficult to cross-link data from registers over time in our studies. This resulted in smaller cohorts, reducing precision. To increase precision and to achieve large numbers of women with TS or Turner karyotype, international multicenter or register-based studies are required over long time periods.
Strengths and limitations

**Strengths and limitations in Paper I**
The strength of this study is the large population-based control group and a fairly large cohort of girls with TS karyotype. The limitations are shortage of data concerning maternal height before 1983, paternal height and age, and data on stillbirths, spontaneous and induced abortions.

**Strengths and limitations in Paper II**
The strength is the relatively large nationwide, register-based cohort of women with Turner karyotype and childbirth and a large control group from the general population. Limitations are the paucity of information on phenotype, indication for karyotyping and mode of conception.

**Strengths and limitations in Paper III**
The strength of this study is the nationwide study in three Nordic countries. To date this is the largest study on deliveries after OD in women with TS. Despite some differences in maternal characteristics and embryo transfer strategy, outcomes were similar in the three countries, supporting generalizability to similar populations. Few data were missing, especially concerning neonatal outcomes. The limitation is the absence of a control group. Denial of OD treatment was not known, thus there might have been a selection of healthier women. Inclusion of women was made by the IVF clinics, and we cannot exclude that some cases may have been missed.

**Strengths and limitations in Paper IV**
The strengths of this study are the register-based design covering all known women with Turner karyotype and childbirth in Sweden and the population-based control group. Limitations are the selection bias, with more healthy women with Turner karyotype giving birth and no data on phenotype.
Conclusions

- No mortality occurred during pregnancy and follow up. Pregnancies among women with TS, especially after OD, carry substantial risks of hypertensive disorders and life-threatening complications, including aortic dissection. Pregnancy did not seem to increase these risks one year or more after delivery.

- Neonatal outcomes were generally reassuring in singletons. Preterm birth rate was higher than in the general population, but the rate of birth defects did not differ.

- Single embryo transfer is strongly recommended in OD.

- Advanced maternal age and short stature were risk factors for women giving birth to a girl with TS. More TS girls were born late preterm and were small for gestational age than non-TS in the general population.
Turner karyotype and childbirth

- Centralized cardiovascular assessment before pregnancy
- Echocardiography/MRI with specific questions: Bicuspid aortic valves, aortic coarctation, aortic dilation, aortic size index in relation to body size
- Pregnancy should be avoided, if cardiovascular or other severe health problems are present
- Tests for thyroid, renal and liver abnormalities and for diabetes
- Single embryo transfer is a strong recommendation
- Pregnancies must be carefully monitored
  - Blood pressure as low as possible
  - Echocardiography/MRI is recommended two to three times during pregnancy
- Consider delivery if complications occur
- Elective Cesarean section is preferable in OD pregnancies if labor does not start spontaneously
- Symptoms must be taken seriously

Aortic dissection is difficult to predict
Future perspectives

9 Childlessness and the possibilities of treating infertility are important research areas in TS. The future possibility of cryopreservation of oocytes and ovarian tissue is to be considered for girls and young women with TS.

9 Placental complications in OD pregnancies need further evaluation and studies to optimize obstetric and neonatal outcomes.

9 Prevention of aortic dissection by intensified antihypertensive medication and oestrogen should be evaluated. The exact mechanism of aortic dissection needs further research.

9 International and national guidelines should be generally implemented and continuously evaluated.

9 Prospective data collected on women with TS and development of international registries for research purposes improves knowledge, clinical care and facilitates future research.
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