ELSEVIER
International Congress Series 1298 (2006) 185 – 189
ICS
www.ics-elsevier.com

Fertility and pregnancy aspects in Turner syndrome

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Abstract. In Turner syndrome, about a third of the diagnosed girls undergoes at least some pubertal development, and up to 5% are fertile. About 50% of Turner syndrome girls have follicles in their ovaries. The likelihood to have them is highest among mosaic Turner syndrome girls who have signs of spontaneous puberty, but also 25% of the non-mosaic Turner girls have them. Hence, cryopreservation of ovarian cortical tissue for infertility treatment in the future is possible. Oocyte donation is an effective option for Turner Syndrome women to obtain children. Pregnancy rates of 30–60% per embryo transfer have been reported. Single embryo transfer is a requirement, because twin pregnancies bear higher risk of pre-eclampsia and impaired glucose tolerance, and Turner women are already a high risk group for such problems. To avoid complications during pregnancies, a cardiology control including magnetic resonance imaging has to be carried out before planned pregnancies. © 2006 Elsevier B.V. All rights reserved.

Keywords: Turner syndrome; Fertility; Ovarian follicles; Oocyte donation; Cryopreservation

1. Ovarian function and spontaneous pregnancies

Normal numbers of eggs develop in girls with Turner syndrome during fetal life, but a majority of them often disappear prematurely [1–3]. The cause is not known, but it has been suggested that the abnormal oocytes without normal second X-chromosome are not viable.

Up to 30% of Turner girls have at least some grade of spontaneous puberty, and some 10% reach menarche, and some 2–5% have been estimated to be fertile [4–6].This may, however, be a too low number. Many of the fertile Turner syndrome women have apparently been undiagnosed. A case report from Sweden [7] demonstrates this.

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doi:10.1016/j.ics.2006.06.004

There are case reports with chromosomal abnormalities among the offspring, and increased incidence of miscarriages among spontaneous pregnancies among Turner women. Turner women with structural abnormalities in one of the X-chromosomes have a risk of mediating this abnormality to their girls [8]. As regards Down's syndrome, only case reports exist. One national survey carried out in Sweden, recognized 77 pregnancies among 25 Turner women. The miscarriage rate was 29% [9].

2. Follicles in the ovaries of Turner syndrome girls

It is not possible to undergo pubertal development without oestrogen secretion. Oestrogen is secreted by the granulosa cells of the ovarian follicles. Hence, there have to be follicles in the ovaries. To show that we carried out a study in Sweden and Finland please refer to [10]. We found follicles in the ovaries of eight out of ten girls aged 11 to 19, who underwent laparoscopy and ovarian tissue freezing, or who underwent oophorectomy because Y-chromosomal mosaicism. There were more follicles in Turner mosaics, and more if the serum FSH concentrations were not elevated above normal range.

To confirm these findings in a larger population and to find out to whom it is meaningful to offer ovarian tissue freezing for preservation of fertility, and at which age, we have now carried out a biopsy to 52 more girls (unpublished). According to our preliminary results, some 50% of these non-selected girls, aged 8–19, had follicles in the ovaries. It seems that mosaic Turner syndrome girls with signs of spontaneous puberty have the highest likelihood in having follicles, and up to 14 years of age does not appear to affect this possibility. However, 25% of the girls with 45 X karyotype had follicles. We are still analyzing the results in more detail, and correlating them to hormone concentrations in order to find a good prognostic score.

It proved difficult to study the chromosomal normality of the ovarian oocytes. They are difficult to isolate without contamination of the other follicular cells, and from tissue sections it is difficult to analyse chromosomes of such large cells in prophase in an accurate way.

3. Cryopreservation of ovarian follicles

Cyopreservation of ovarian follicles within the ovarian cortical tissue is technically feasible, and normal function of such tissue has been shown [11].

The method is widely applied in young women facing chemotherapy, and children have been born to these after transplantation of frozen–thawed tissue to the pelvic wall or ovary [12,13].

Technically, cryopreservation of small slices of ovarian tissue obtained laparoscopically from Turner girls is not problematic. To know who has enough follicles to become pregnant after transplantation, we are now analysing the results from our larger population. We are also developing an in vitro maturation system to obtain mature oocytes from the follicles, although we have not yet succeeded in doing so.

It is not desirable to take too much tissue in the biopsy, because taking a whole ovary might reduce the possibilities of spontaneous pregnancies in the future. One of the Turner

girls who had follicles in her biopsy tissue at the age of twelve years, became spontaneously pregnant when she was 18, and gave birth to a healthy infant.

But if we do not offer a possibility of cryopreservation to these young girls they do not have a possibility for giving birth to biological children if we are able to develop an effective system to mature oocytes later on.

If oophorectomy is still carried out to Turner girls because of a risk of gonadoblastoma who have a marker Y-chromosome, this tissue should be cryopreserved for possible maturation of oocytes in vitro. Another and probably better option would be to wait and control the young woman until she has obtained her children before the oophorectomy is carried out.

4. Oocyte donation in Turner syndrome

Oocyte donation has been used among women with Turner syndrome since the treatment became available in the mid-1980s [14]. At the beginning, the pregnancy results were not as good as they were among other women with ovarian failure [15,16], and some inherent problems in the endometrium were suspected. But larger surveys later on have resulted in similar pregnancy rates as are obtained among other women with ovarian failure [17–21]. Also the high miscarriage rates have been reduced, probably due to more adequate hormonal replacement therapy.

The pregnancy rates per embryo transfer have varied in these more recent surveys from 30–60% (Table 1). In Sweden, oocyte donation became legal in 2003, and we could begin these treatments in Turner syndrome women. Seven Turner women have been treated with 10 fresh and five frozen thawed single embryo transfers, and three healthy infants have been born.

High blood pressure is a problem in oocyte donation pregnancies affecting up to 30% of the recipients [22,23], and the same problem has been encountered among Turner syndrome women. In a Finnish survey [19], six out of fourteen women had hypertension during pregnancy, one of them with severe pre-eclampsia and growth retardation of the infant. In a survey by Bodri et al. [21] five out of nine women had hypertension and pre-eclampsia was noted in three of them. Five infants were growth retarded, among them a set of twins.

Turner syndrome women have also other risk factors but hypertension. Aortic dissection is a severe complication, affecting some 2% of these women per year [24]. A pregnancy does not reduce the risk, but it might increase it among women who have aortic dilatation.

Table 1
Pregnancy results in Turner syndrome after oocyte donation

Article	No. of women	No. of ET	Embryos/ET	Pregnancies	Miscarriages
Ref. [15]	6			2	
Ref. [16]	22	58	3.1	14 (23%)	5 (36%)
Ref. [17]	11	25		6 (24%)	3 (50%)
Ref. [18]	29	68	Up to 3	28 (41%), 2 triplets	14 (50%)
Ref. [19]	18	33	1.5	22 (67%), 1 twins	8 (36%)
Ref. [20]	9	15		5	2 (40%)
Ref. [21]	21	30	1–4	12 (40%)	3 (25%)

Careful diagnostics using magnetic resonance imaging before a planned pregnancy is definitely indicated.

Taking into account these two risk factors, and maybe increased risk of impaired glucose tolerance, the additional risk of twin pregnancies cannot be taken among these women. Single embryo transfer is a requirement. A good quality embryo cryopreservation programme guarantees that the likelihood of pregnancy per oocyte donation is similar if one or two embryos are transferred at a time.

Adequate hormonal replacement therapy, preferably four to six months before the planned embryo transfer is recommended to optimize the uterus for pregnancy. Miscarriages can probably be avoided by doing this [19].

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