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Pregnancies in XY women: Is a weak myometrium cause of complications during pregnancy and delivery?

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ABSTRACT

Two 46, XY women with Swyers syndrome: A 39 years old with a normal twin pregnancy and a 26 year old with a singleton pregnancy and uterine rupture in the 2nd trimester. A woman with Swyer syndrome carried a twin pregnancy and delivered by caesarean section, while another Swyer syndrome patient with a singleton showed uterine rupture gestation week 20. These results and the present literature with only about 20% vaginal deliveries may suggest that the uterus of the 46, XY women might be weak and unable to contract compared to uterine muscles in normal women due to its hypoplastic nature.

1. Introduction

Women with 46,XY karyotype are usually diagnosed in the teenage years due to delayed puberty and primary amenorrhea. In Denmark 200 women have been registered in the national Danish Cytogenetic Centralregister as having a 46,XY karyotype. Based on this registry and the population of two million women in the late teenage years or older in Denmark, the prevalence is one XY-woman in 10.000 women. The condition may be caused by either gonadal dysgenesis due to failure in male sex determination (Swyer syndrome) or defective androgen receptors (Morris syndrome)[1]. If 1/3 of XY-women have Swyer syndrome as suggested by Michala et al.[2], there seems to be a huge potential for pregnancies with oocytes donated by other women, since patients with Swyer syndrome usually have a uterus, although hypoplastic.

However, only very few pregnancies are described in literature [2-17]. Here we report two pregnancies in XY-women: one successfully ending with birth of two healthy twins by caesarean section (CS) and one unsuccessfully ending dramatically with uterine rupture in gestational week 20.

2. Case 1

The patient, a Caucasian woman, was referred because of amenorrhea at 17 years of age. She had a height of 183 cm and a weight of 67 kg. Phenotypically she was hypoestrogenic with a small uterus, a small, tenon-shaped portio, and a pale hypoestrogenic vaginal mucosa. The breasts were not developed (Tanner 1). The patient has a dizygotic twin, who had normal menstruation and no gynaecological-obstetrical problems.

She was diagnosed with a pure 46,XY karyotype (blood cells) and subsequently she had a bilateral laparoscopic gonadectomy, an appendectomy, and a unilateral salpingectomy. Cyclic estrogene-progesterone treatment was started, and after eight months of treatment the depth of the uterine cavity was measured to 6 cm using a sound.

The hormonal treatment was continued for the following years and at the age of 39 years she was referred for *in vitro* fertilization (IVF) with donated oocytes from an anonymous volunteer and fertilized with her husbands sperm. During the treatment cycles she had estradiol (Femanest, Sandoz, Odense, Denmark) 2 mg 3 times a day from the 2nd menstruation day, and when the endometrium was at least 8 mm, we supplemented with vaginal capsules of progesterone (Progestan 100 mg × 4, Besins-Iscovesco,

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Paris, France) from three days before embryo transfer. Between the respective treatments she was given a cyclic three-stage estradiol (up to 4 mg)-norethisteroneacetat treatment (Trisekvens Forte, Novo Nordisk, Copenhagen, Denmark).

Following three IVF cycles with embryo transfer, resulting in a biochemical pregnancy, a twin pregnancy was achieved in the fourth attempt. During the first two attempts, a four-cell and, in the second attempt, a five- and an eight-cell were transferred day 2 and 3, respectively. In the third attempt an eight cell was transferred day 3 resulting in an s-hCG of 181 IU 15 days later. However, an ultrasonography at week seven showed a blighted ovum, 4.5 mm of size, and the patient aborted spontaneously. In a fourth attempt, five oocytes were received by donation, 4 were fertilized and three divided to be acceptable for transfer. An eight- and a seven-cell were transferred, while a six-cell was cryopreserved. Seventeen days later a positive urine-hCG (Clearblue) was measured, and in the seventh gestational week two living embryos were detected inside the uterus.

Treatment with estrogene and progesterone was continued until gestational week 13. The pregnancy was uncomplicated, and week 38 she delivered two healthy children by CS due to maternal request: a girl with a birth weight of 3 130 g and a boy with a birth weight of 3 550 g. At delivery the patient had a height of 192 cm and a weight of 90 kg.

3. Case 2

A now 26 year old Caucasian women was diagnosed as having a 46, XY karyotype had a bilateral gonadectomy and bilateral salpingectomy when she was 16. She then had a height of 165 cm and a weight of 51 kg (BMI=18.7). At 18 years she started treatment with cyclic estrogene-gestagene (Trisekvens, Novo Nordisk, Copenhagen, Denmark). Unfortunately, we have no information of the size or depth of the uterus during early hormone treatment, but the uterus is described as normal by ultrasonography.

She started IVF, and in the second embryo transfer attempt two four-cell embryos were transferred two days after aspiration of oocytes from an anonymous donor. Pregnancy was achieved, and as in case 1, estrogene-progesterone substitution treatment was given during the first 12 weeks of gestation to support the pregnancy.

The patient was admitted to the local hospital at 18 1/7 weeks of gestation presenting with acute-onset severe abdominal pain. An acute appendicitis was suggested, but at laparoscopy 2 liters of blood coming from a fundal defect of the uterus was found in the peritoneal cavity. Ultrasonography performed during the operation showed an unaffected fetus with normal heart beat, and the thickness of the uterine wall was measured to 3.5 mm. Hemostasis was obtained by covering the defect with TachoSil (Takeda International, Zûrich, Switzerland) in the defect. Hemoglobin concentration raised from 4.2 mmol/L to 6.2 mmol/L after infusion of two portions of erythrocyte suspension, and the patient was transferred to the university hospital.

After 12 days of hospitalization here, the patient had a new episode of severe abdominal pain with hypotension (blood pressure: 65/50 mm Hg). Abdominal ultrasonography showed large amounts of fluid below the diaphragma, and the fetus still with demonstrable heart action was seen in the upper abdominal cavity outside the uterus. At emergency laparotomy the fundal region of the uterus was ruptured, and 1800 mL of blood was found intraabdominally. A dead female fetus (24 cm, 267 g) was removed from the abdomen. The placenta weighting 114 g was still inserted inside the uterus. A hysterectomy was performed and the patient recovered uneventfully (Figure 1).

4. Discussion

The present paper describes two pregnancies in women with pure 46,XY gonadal dysgenesis. In one case twins were delivered by CS at week 38, while in the other case the patient presented with uterine rupture in gestation week 18. In literature only 25 pregnancies including the present two, are described (Table 1) with twenty-one leading to delivery of at least one living child. The children were born by sixteen women as two women had a singleton pregnancy followed by a twin pregnancy and one woman gave birth to

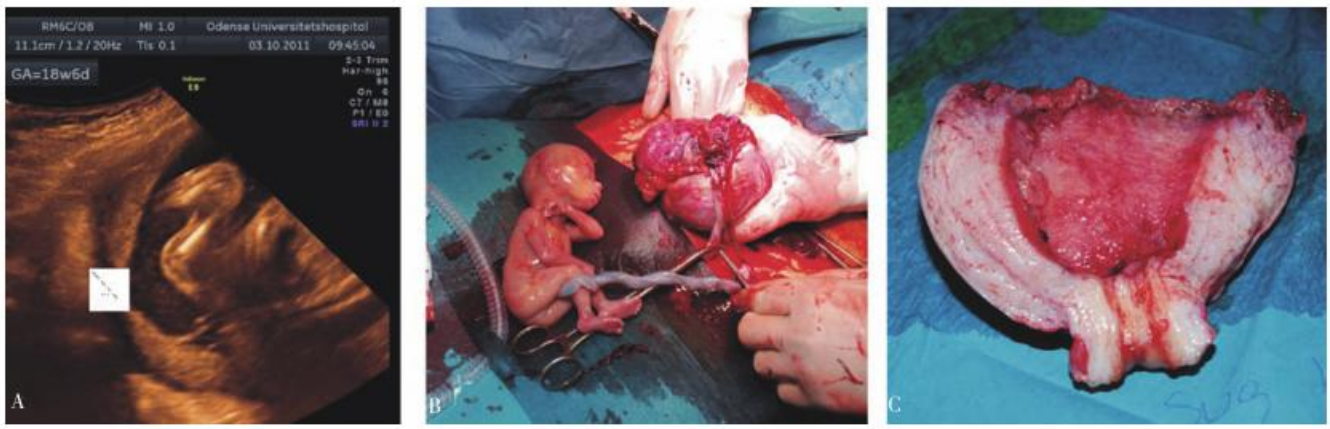

Figure 1. Uterine rupture in pregnant 46,XY woman gestational week 20.
A: Ultrasonography showing a thin (5.4 mm) fundal uterine wall a few days before uterine rupture (Photo: *Lene Sperling*). B: The fetus and the big defect in the fundal part of the uterus. The female fetus had a weight of 267g and a length of 24cm. C: The uterus with the big defect cut open (*Photos b&c: Kresten Rubeck Petersen*).
*The patient has accepted that these photos are published.

two singletons (Table 1).

Rupture of the uterus during pregnancy is rare. It may be caused by intrinsic factors (grand multiparity, malpresentation, placenta accreta, or uterine anomalies), iatrogenic factors (previous CS, myomectomia, internal podalic version or fundal pressure for labor dystocia), or appear spontaneously without known intrinsic or iatrogenic etiologies [18]. Uterine ruptures occur in 1:16.849 [19] to 1:19.765 deliveries [20] in women without a previous CS. In the 2nd trimester uterine rupture occurs even more seldom, so the present case story is very unique.

It might be relevant to compare pregnancy outcome in 46,XY women with those in 45,X0 women since both have only one X chromosome. Pregnancy in women with Turner women (45,X0 karyotype) may be complicated by congenital cardiac malformations such as bicuspid aortic valve, coarctation and/or aneurysm of the aorta which are found in 25%–50%. Likewise hypertension occurs in 40%–50% of pregnant women with Turner syndrome, who are known also to have increased maternal cardiovascular mortality due to aorta dissection and rupture. Furthermore, 1/3 of Turner women have urinary system abnormalities (horseshoe kidney) and approximately half have Hashimoto's thyroiditis and may be hypothyroid, which may complicate their pregnancy [21, 22].

None of the published reports of pregnancies in 46,XY women describe an examination programme prior to treatment with donor-oocytes (Table 1) and congenital malformations of the cardiovascular or urinary systems or thyroid disease have not been described in these pregnant women. Hypertensive disorders have, however, been described in two singleton pregnancies either diagnosed pregestionally [16] or in gestation week 33 [8]. Both cases were without concomitant proteinuria, but led to fetal stress indicating CS in gestation week 38 and 33. In the last case, a second pregnancy was ended by a CS due to twins, previous

Table 1

Mode of delivery and indications for Caesarean section in 46,XY women arranged chronological and in relation to geographical localization.

Geographical localizationand year	Singleton or multiple pregnancy	Mode of delivery & Gestational week	Indication for Caesarean section	No of living children born	Comments	Reference
France, 1988	Singleton	1INA	INA	INA	Ongoing, gest. week 30	3
California, 1989	Twins	[2]CS, w. 35	Preeclampsia	2		4
France,1990	Abortion + Full term	CS		INA		5
	INA	INA	INA	INA	Ongoing	
New Jersey, 1990	Triplets	INA	INA	3?	45,X/46,XY	6
Italy, 1992	INA	INA	INA	INA		7
Iceland,1997	Singleton + twins	CS, w.33+36	Gest. Hypertension +[3]Failed labor induction	1(boy)+2(boys)	ZIFT/ZIFT	8
Israel, 2000	[4]Twins + twins	CS, w. 41+40		1+2		9
India, 2002	Singleton	CS	[3]Failed labor induction	1(boy)	GIFT	10
Taiwan, 2005	Twins	CS, w. 36	Fetal malpresentation	2(boys)	Gonadoblastoma +germ cell tumor	11
Taiwan, 2007	Twins + mole	CS, w. 33	Hydatiform mole + Preeclampsia	2		12
North Carolina, 2008	Singleton	CS,	Marginal cord insertion	1(girl)	[5]FER	13
UK, 2008	Singleton	vaginal		1(girl)		
UK, 2008	Singleton	CS, w. 36	Preeclampsia	1		2
	Singleton+singleton	vaginal+vaginal		1+1		
	Singleton	vaginal		1		
Serbia, 2011	Singleton	CS, w.39	Breech presentation	1		15
Greece, 2011	Singleton	CS, w.38	Fetal stress, growth retardation & oligohydramnios	1(boy)		16
China, 2011	Twins	CS, w.36		2(girls)	Vitrified oocytes	17
Denmark, 2012	Twins Singleton	CS, w.38	Maternal request	1(girl)+1(boy) 0	Uterine rupture 2nd trimester	Present study

[1]Information not available.
[2]Caesarean section.
[3]Failed induction of labor with prostaglandin vaginal pessaries and oxytocin.
[4]One fetus demised spontaneously at week 19 of pregnancy.
[5]Treatment with frozen-thawed embryos.

CS and slightly increased blood pressure [8]. In two twin pregnancies and one singleton pregnancy, CS was performed in gestational week 33 [12], week 35 [4], or week 36 [2] due to severe preeclampsia with increased blood pressure and proteinuria.

Generally, a high Caesarean rate was observed in the reported pregnancies of Swyer patients. According to Table 1, 67% [8] of 12 singletons were delivered by CS, and 82% [18] of 22 pregnancies in total were ended by a CS. This is very close to a 80% Caesarean section rate found after treatment of Turner patients with donated oocytes in a Swedish study [23]. This high CS rate in XY women might be due to a high rate of multiple pregnancies (36% ~8/12). Other factors are high blood pressure/preeclampsia in 5 women (6 pregnancies), including 3 multiple pregnancies, as described above. In two cases (twin & singleton) fetal malpresentation indicated CS (11, 15; Table 1). It seems that the pelvis, which may be android, has in no case (maybe except 9 and 5) been exactly measured/evaluated. Furthermore, it cannot be excluded that particular care has been given to this group of patients, or publication bias tending to report the most pathological cases might have occurred.

It is still an open question whether the hypoplastic nature of the uterus might contribute to the high rate of CS in patients with Swyers syndrome. Thus, at least in some cases CS was performed after failed induction of labour with prostaglandin vaginal pessaries and oxytocin given i.v. [8, 16] suggesting a reduced ability of the uterus to contract upon hormonal stimulation. In addition, our second case with uterine rupture in the mid-trimester indicates the presence of an anatomical weakness of the uterus. This could not be detected by vaginal ultrasonography performed before stimulation for embryo transfer.

Since women with Swyers syndrome have a uterus but usually do not produce germ cells, they are able to wear a pregnancy but not to be one of the biological parents. However, it has been possible for a 46,XY true hermaphrodite to father a monozygotic twin pregnancy. During childhood this patient underwent genitalia reconstruction, right orchiopexy and left salpingo-oophorectomy revealing a gonadoblastoma [24].

Although the uterus in 46,XY women is usually hypoplastic before hormonal treatment, several successful pregnancies, including multiple pregnancies, are described. However, in only about 20% of the reported cases the women gave rise to vaginal birth, and furthermore we here describe one case with a spontaneously uterine rupture in the 2nd trimester, which is a very rare condition.

Such information may suggest that the uterine wall might be weaker and with a reduced ability to contract compared to normal uterine walls. In the future it might be interesting and clinically relevant to evaluate the thickness of the endometrium by MR imaging, including directions of the muscle fibres by socalled MR diffusion tensor imaging [25] to evaluate if it would be possible to predict risk of uterine rupture.

The authors declare no conflicts of interest.

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