First successful ovarian cortex allotransplant to a Turner syndrome patient requiring immunosuppression: wide implications

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Objective: To determine whether we can safely and successfully transplant an ovary tissue allograft from a nonidentical donor to her Turner syndrome sister.
Design: Transplantation of cryopreserved ovary tissue, as well as fresh transplantation of ovarian tissue between identical twins, is now well established with numerous reported successful cases. However, there have not yet been any ovary transplants between nonidentical women requiring immunosuppression (ovary allotransplant). This could be a much more common indication for ovary tissue transplantation if safe and reliable immunosuppression were available.
Patient(s): A 20-year-old amenorrheic woman with nonmosaic 45-XO Turner syndrome requested ovary tissue transplantation from her fertile 22-year-old 46-XX sister. They were an human leukocyte antigens match but were ABO incompatible, a well-known contraindication to solid tissue or organ transplantation. The Turner syndrome sister strongly preferred to be able to become pregnant naturally without donor egg in vitro fertilization and to avoid hormone replacement therapy. In her religious group, that would also be important for finding a marital match. Despite the poor prognosis associated with ABO incompatibility, an ovary from her 22-year-old nonidentical fertile sister was transplanted to her employing the immunosuppression protocol now used for kidney transplant patients in our centers at Washington University and Johns Hopkins.
Intervention(s): Not applicable.
Main Outcome Measure(s): Post operatively at 5 months she developed normal monthly menstrual ovarian function, and she became spontaneously pregnant with a normal infant girl. The relation between her postoperation follicle stimulating hormone and antimüllerian hormone levels continue to support the theory that tissue pressure controls primordial follicle recruitment. The fact that ABO incompatibility did not prevent success suggests that diffusion and not revascularization may be all that is required for successful long-term ovarian cortex transplant survival with spontaneous pregnancy.
Result(s): Ovary allotransplantation with safe immunosuppression allows natural conception, and also normal hormone function obviates the need for hormone replacement therapy. Orthotopic placement of the graft and surgical technique is critical for natural conception and a higher pregnancy rate.
Conclusion(s): Allotransplantation requiring safe immunosuppression, if successful, maybe a much more commonly used indication for ovary transplantation in the future than frozen ovary grafts or grafts between identical twins. (Fertil Steril® 2025;123:156–63. ©2024 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Turner syndrome case report, ovary allotransplant, safe immunosuppression, ovarian failure

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Young women with Turner syndrome have been unable to have children without the use of donor egg in vitro fertilization (IVF). However, egg donation is not accepted in some religions, and most Turner syndrome women would prefer to have normal hormonal function and to become pregnant naturally without IVF. These issues can be overcome by ovarian tissue allotransplantation if we could employ a safe immunosuppression protocol similar to uterine transplantation (1, 2). After a successful ovary allotransplant, hormonal function would obviate the need for hormone replacement therapy (HRT), and pregnancy could occur naturally from the transplanted ovary tissue through intercourse rather than with donor egg IVF. For many young patients, it is preferable not to have to dwell on donor egg IVF when discussing family building with a future mate.

For donor selection, one would prefer an human leukocyte antigens (HLA) match and ABO compatibility. However, if a perfect immune match were not required, there would be a much wider spectrum of possible ovarian tissue donors and ovary transplantation could have much wider use for all women with premature ovarian failure (POF). ABO incompatibility is considered an absolute contra-indication for a solid organ or tissue transplant, which requires revascularization (3, 4). However, if there were ABO incompatibility, and the ovary graft survived, this would indicate that ovary cortical tissue grafts may possibly survive on diffusion alone without the need for revascularization.

An ovarian cortical tissue allotransplantation from a nonidentical donor requires a safe immunosuppression protocol because it is not a life saving procedure. Previous large reports of kidney transplant patients on long-term immunosuppression at Washington University and Johns Hopkins allowed us to conclude that ovarian allotransplantation could be safe both for the Turner syndrome patient and for their offspring as well as any other POF (5–8). We decided to emphasize very low or zero steroid administration after the day of the allotransplant because long-term corticosteroid use is the major danger of immunosuppression for transplant patients.

CASE REPORT

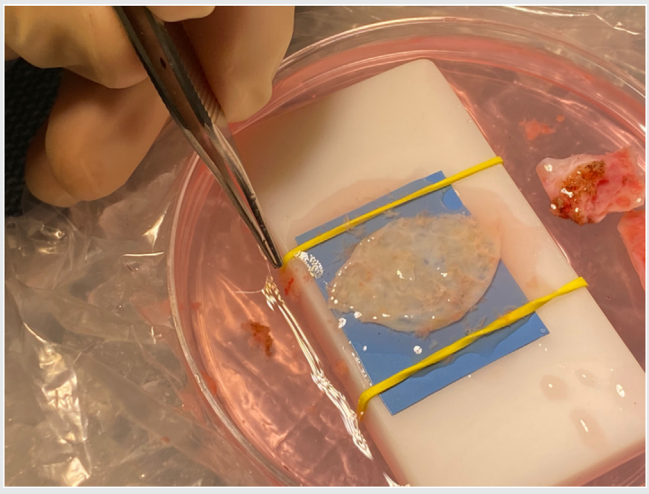
First case

A 20-year-old woman with nonmosaic 45-XO Turner syndrome was amenorrheic with an antimüllerian hormone (AMH) of 0.015 ng/mL, and an follicle stimulating hormone (FSH) of 67 mIU/mL. Her 22-year-old 46-XX sister already had two children, normal menses, and an AMH of 4.97. They were HLA identical but ABO incompatible (Supplemental Table 1, available online). Both sisters possessed HLA of A: 03:02, B: 08:01, C: 04:01, and DRB1: 03:01. The Turner syndrome sister was Rh: O+, and the donor sister was Rh: A+. This was deemed a contra-indication to a solid tissue transplant because revascularization would be impossible (3, 4). There were no other donors available. According to their religious views, donor oocyte IVF is not allowed, but ovary tissue allotransplant would be allowed. Furthermore, the Turner syndrome sister by far preferred to be able to get pregnant naturally without donor egg IVF, and did not want to require HRT (hormone replacement therapy). In addition, in their religious group, having a functioning ovary would make it much easier to find a good marital match. Without a functioning ovary and the ability to have an infant, she would never be able to find a good marital match. The Turner syndrome recipient was fully evaluated for cardiovascular issues as well as an entire workup to make certain pregnancy would not put her at increased risk. She was found to be completely normal except for reduced height (9, 10). Informed consent was obtained from the donor and recipient after proper counseling, and Institutional Review Board (IRB) approval, including the experimental nature of the approach. The entire IRB from beginning to current is attached in supplement. Additionally, consent was obtained from the donor and recipient for publication of this case report. She also went under intense rabbinical ethical review. The three Haredi experts in Jewish ethics had referred her to us and had reviewed the case to the extreme, and formally approved of ovarian allotransplant. They still approve and are referring more patients with POF for ovary allotransplant.

The left ovary of the donor was removed and dissected (11–17). One-third of the cortex was transplanted to the right streak ovary of the recipient and the remaining two-thirds were cryopreserved (Figs. 1 and 2). At the same time, germinal vesicle oocytes in the spent media after cortical dissection were cultured for in vitro maturation (IVM) (17, 18). The immunosuppression protocol consisted of a huge dose of methylprednisolone (7mg/kg intravenous) only on the morning of surgery along with antithymocyte globulin (3mg/kg intravenous), and for maintenance, tacrolimus (3 mg orally twice a day) with a target trough of 5–10 ng/mL (eventually to be discontinued), azathioprine (100 mg orally), and prednisone only (5 mg orally or by mouth daily) (never to be increased), with tacrolimus eventually to be discontinued (Supplemental Table 2). Post operatively she was followed with hormone levels and ultrasound monthly, as well as tacrolimus levels, and blood cell counts as indicated. The patient received induction and maintenance immunosuppression similar to that used for renal transplantation at Johns Hopkins and Washington University (19).

By 168 days postoperation, the Turner syndrome recipient was menstruating normally and her FSH had reduced to 9.13 mIU/mL, with no signs of rejection. Her menstruation and ovulation continued monthly. Her AMH began to rise at 168 days from 0.05 to $\leq$0.35 mg/mL at 223 days, typical for a successful ovary cortical graft. This AMH level after frozen ovary tissue autografts is consistent with 8–10 years of expected function because the rate of primordial follicle recruitment is reduced when ovarian reserve is reduced (16, 17, 20). The allograft continued to function normally with monthly menstruation. Six months later (11 months postoperation) her uterus grew from infantile to that of a normal adult (Supplemental Fig. 1, available online). The Turner syndrome recipient continued to menstruate monthly and became spontaneously pregnant 1.5 years postoperation, 7 months after her uterus had grown to that of a mature adult. Her 7-week ultrasound showed a normal sac and normal fetal heart rate (Supplemental Fig. 2), her 21-week ultrasound showed a normal infant girl and she also had a normal

FIGURE 1



The ovary cortex of the donor was dissected from the medulla down to a thickness of only 1 mm. The spent media after this dissection is examined for cumulous complexes and all GV's are cultured over 24–48 hours for IVM. GV = germinal vesicle; IVM = in vitro maturation.

Silber. Ovarian cortex allotransplant for Turner. Fertil Steril 2025.

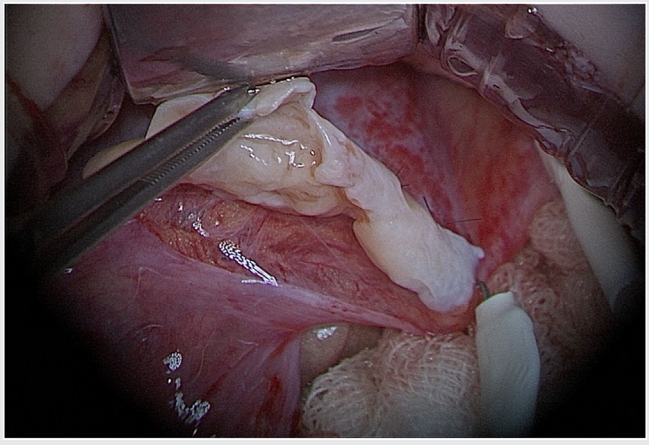
33-week ultrasound showing a normal infant girl. She delivered in June 2024 a healthy infant girl 2.6 kg at 40 weeks and 2 days (Fig. 3).

The graph of her AMH and FSH levels postoperation is similar to graphs we have already reported for both fresh and frozen ovary tissue transplants that were not allografts (Fig. 4) (21, 22). The FSH comes down to normal by 4–5 months, as the AMH goes up to high levels, and then recedes down to very low levels, which we have shown does not prevent long-term functioning of the graft (16, 17, 20, 23). The donor FSH was 6.8 mIU/mL, unchanged from preoperation, she continued menstruating normally and became spontaneously pregnant with her third child (despite having an intrauterine device in place) by 6 months postoperation and delivered her third healthy infant (indicating her ovary donation did not reduce her fertility).

DISCUSSION

Both fresh and frozen ovary cortical tissue transplants have been performed successfully in sheep in 1994, and in humans beginning in 2004 with many healthy infants (11–17, 24–26). However, these have either been frozen autotransplants or identical twins, with no need for immunosuppression.

FIGURE 2



The donor ovarian cortex is then transplanted to the medulla of the recipient ovary after the recipient cortex is resected. 9-0 nylon sutures are used under ×10–16 magnification, and there is continuous irrigation with pulsatile heparinized saline to prevent adhesions.

Silber. Ovarian cortex allotransplant for Turner. Fertil Steril 2025.

FIGURE 3

Healthy infant girl delivered at 40 weeks and 2 days, 2.6 kg.

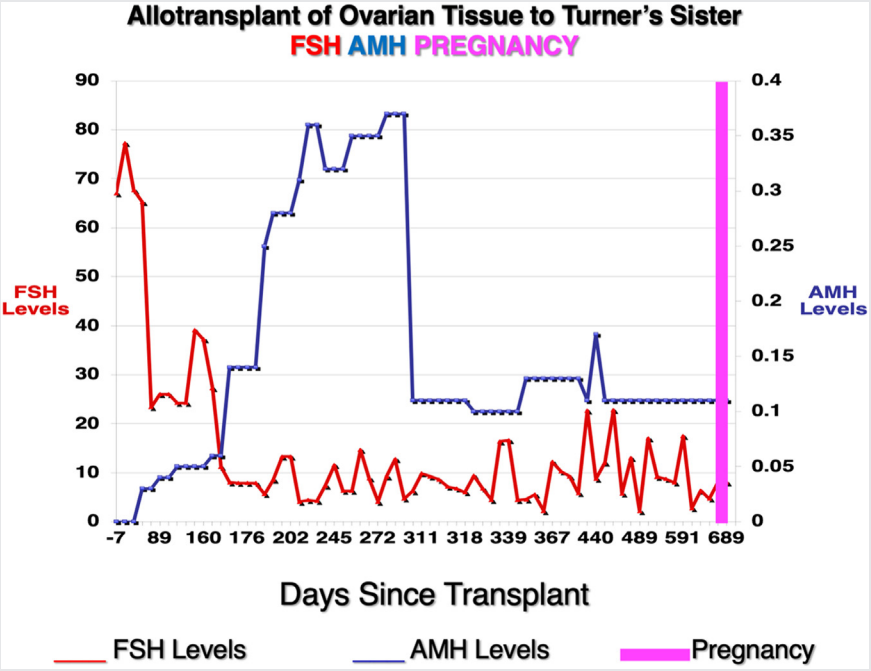
Silber. Ovarian cortex allotransplant for Turner. Fertil Steril 2025.

Identical twins discordant for low or no ovarian reserve are quite rare and although they represent a fascinating series, there are no widespread clinical benefits (12–14). Frozen autotransplants are a more common indication, and they also do not require immunosuppression (11–17, 24–26). For cancer patients whose tissue was frozen before their chemotherapy or bone marrow transplant Allogeneic Hematopoietic Stem Cell Translation, the issue of concern has been risk of transferring cancer cells with the transplant. However, fortunately, that has not yet been found to be a problem (27).

Note that even frozen autotransplants can undergo immune rejection, which requires us to understand the difference between allotransplant and homotransplant. Allotransplant requires immunosuppression and homotransplant does not. If a cancer patient has had a bone marrow transplant from another donor, her bone marrow immune cells will not be that of her transplanted tissue (28). If her transplanted bone marrow cells have become completely tolerant to her original tissue, then the transplant of her previously frozen tissue will not be rejected. However, if she has any degree of residual graft vs. host disease immunity with incomplete tolerance, she will reject her own frozen ovary graft.

In our center alone, there have been many healthy infants born from either fresh identical twin ovary homotransplants or frozen ovary autotransplants with no complications and with long-term graft survival (11–17). They required no immunosuppression. However, one case with minor graft vs. host from her bone marrow transplant was rejected. Nonetheless, for women who never had their ovary tissue cryopreserved before they became sterile, or for patients with Turner syndrome, or any POF, ovary allotransplant with safe immunosuppression would be a favorable option. In fact, ovary allotransplantation might become the most common indication for ovary tissue transplantation. Identical twins discordant for ovarian function are rare, and the majority of young cancer patients have not undergone ovary cryopreservation. Since there have been many thousands of kidney transplant patients on immunosuppression who had successful pregnancies, it only seemed reasonable that women could have a normal pregnancy and birth after ovary or uterine transplantation using a safe immunosuppression protocol (5–7).

FIGURE 4



As the FSH came down to normal levels by 3–5 months, at the same time the AMH began to rise to high levels. At 10 months postoperation, the AMH reduced to lower levels and remained stable at those levels. At 23 months postoperation, the recipient became spontaneously pregnant. The relationship between the decline of FSH and the rise and fall of AMH is the same as has been seen in all fresh and frozen ovary cortical transplants and indicates an over-recruitment of primordial follicles from decrease in pressure at the time of transplant with partial depletion of primordial follicles. AMH = antimüllerian hormone; FSH = follicle stimulating hormone.

Silber. Ovarian cortex allotransplant for Turner. Fertil Steril 2025.

There are several unique paradigm shifts that derive from this report. First, for solid tissue transplants, ABO compatibility is always required to prevent immediate devascularization, breakdown, and hyperacute loss of the graft (3,4). This sister-sister donor/recipient match was HLA compatible but ABO incompatible, and would normally be rejected for any allotransplant. Bone marrow transplant is different in that we know they survive on diffusion. However, there was an unknown possibility that perhaps an ovary tissue graft might survive on diffusion alone, so the patient elected to have an ovary tissue transplant from her nonidentical sister despite the poor prognosis. In addition, they were hopeful that even if the transplant failed we could nonetheless obtain oocytes from the graft, and perform successful IVM. These oocytes would be considered by her religious beliefs to be the recipients because they would come from the transplanted tissue. The robust success of this transplant suggests that ovary cortical tissue transplants may possibly survive quite well on diffusion alone with no need for revascularization.

A second point is that removing an entire ovary from the donor did not impair her fertility (20). She became pregnant spontaneously, within 6 months despite having a Mirena intrauterine device in place, and she delivered a healthy infant. If you remove an entire ovary from a young woman, the average age of menopause is only reduced by one year (from 51 to 50 years) (20). Indeed, as a woman ages, she has a dramatically reduced ovarian reserve in her 30's but her eggs are not totally depleted for another 15 years. We have previously reported that despite a very low AMH, these ovary tissue grafts can last 10 or more years (11, 15–17, 23). This is why it has been suggested by Andersen that by grafting frozen tissue every decade a woman may avoid ever having menopause (21–23).

A third point is that with such a safe immunosuppression protocol, ovary transplants and uterine transplants, that are not "life saving" can be employed for patients with Turner syndrome or other causes of ovarian failure (of course with proper IRB approval). Our experiences from this case and our previously reported identical twin fresh ovary transplant series tell us that patients prefer this treatment to the prospect of HRT and donor egg IVF cycles.

It should be noted that "nonmosaic" XO Turner syndrome patients must actually be mosaics (even if their karyotype testing shows pure XO), or else they would not be alive. X genes that escape X inactivation have Y homologs that allow males to survive even with only one X chromosome (29). But without a Y chromosome, two X chromosomes must be present in some of the cells for the XO Turner syndrome girl to survive (30). A total of 99% of XO Turner syndrome pregnancies miscarry. Those are the ones that are true 100% pure XO Turner syndrome. Those who do not miscarry must have two X's in some of their cells. Nonetheless, the vast majority of Turner syndrome women, whether "mosaics" or pure XO (meaning that there was only one X seen on clinical

karyotyping), undergo POF and cannot conceive without either their own eggs frozen before or early in puberty, or with donor eggs or donor ovary allotransplant (31, 32).

Aside from the immediate benefit of ovary allotransplantation to Turner syndrome women, and to any women with POF of any cause, this is what we have learned scientifically. First, safe immunosuppression protocols that eliminate long-term corticosteroids allow us to consider allotransplantation for nonlife saving reasons. Uterine transplantation and ovary transplantation fall into that category. Second, we now realize that ovary cortical grafts may survive on diffusion alone, and revascularization may not be required. Of course, Turner syndrome patients must have a complete vascular evaluation to make sure it is safe for them to get pregnant, but most will pass this requirement. All would prefer natural conception and normal hormonal function to donor eggs and HRT. Particularly for women of certain religions, it will be very difficult to marry when you have to reveal you will need donor eggs, rather than you are fertile and normal as a result of having had an ovarian tissue transplant.

One factor that influenced this family's decision to go ahead with the transplant despite ABO incompatibility was that we could IVM germinal vesicle oocytes derived from the removed and transplanted ovarian tissue, and vitrify them once they reach metaphase II stage (17, 18, 23–36). The technique and result for this have already been described in detail.

Finally, the surgical technique is an important factor in the success or failure of ovary tissue transplants. The cortex is dissected very thin down to only 1 mm thickness. It is placed on top of the medulla after the peritoneal surface of the streak ovary is removed and sutured with 9-0 nylon interrupted to fix it in place and prevent the formation of micro-hematoma underneath the graft. Continuous pulsatile irrigation with heparinized saline is employed to avoid adhesion formation. With this technique, such grafts have been reported to last $\leq$10 or more years (16–18). It is crucial that the transplanted ovary tissue is placed in a position where the Fallopian tube can pick up the ovulated oocyte on its own. More importantly, natural pregnancy is much more successful in ovary transplant cases than IVF where very few if any eggs are retrievable. With IVF, you will not obtain more than one or two oocytes. But if the ovary graft is placed in a position where the one ovulated oocyte every month can be picked up by the Fallopian tube, then clearly a pregnancy is much more likely. Our pregnancy rate leading to healthy live births before this case is 78%, and all have been natural, none from IVF (16–18).

Over 9 years, we reported the timing of FSH and AMH levels postoperation, and postulated that it takes 4–5 months after primordial follicle recruitment for oocytes to become sensitive to gonadotropins and enter the ovulatory menstrual cycle (21, 22). That is, when the FSH goes down and the AMH climbs to extremely high levels before returning to very low levels (Fig. 4). We interpreted that there is an over-recruitment of primordial follicles right after the transplant caused by a reduction in ovarian cortical tissue pressure. That is why 4–5 months later the AMH climbs to high levels, but then 4–5 months after that, the AMH declines to very low levels (21, 22). This concept was supported later by in vitro oogenesis studies in the mouse (37, 38). Comparatively, the 4–5 months in humans for recruited follicles to become gonadotropin sensitive is only 3 weeks in the mouse and is called the in vitro differentiation phase (37, 38). In vitro-produced oocytes will become quiescent if cultured under high atmospheric pressure, but will be recruited if cultured at normal atmospheric pressure (18, 38). Thus the entire regulation of primordial follicle arrest and recruitment is controlled by tissue pressure gradients. Therefore, it has been deduced that oocytes after transplant are not lost because of ischemia, but rather are lost because of over-recruitment of otherwise locked primordial follicles due to the reduction in tissue pressure.

The rate of primordial follicle recruitment is reduced when the number of primordial follicles (ovarian reserve) is reduced? Whenever we are transplanting or cryopreserving tissue from older women or women with lower ovarian reserve the ovarian cortex is seen to be thicker and the tissue more dense because there are fewer follicles dispersed through the fibrous tissue of the cortex (Supplemental Fig. 3A–C). This tissue pressure gradient regulates recruitment and indeed protects the ovary from allowing all of the oocytes to continue in meiosis in the fetus and then degenerate in a matter of months, which would otherwise completely deplete the ovary of eggs before birth. When the tissue pressure gradient is denser, primordial follicle recruitment is reduced. That is why despite a very low AMH these transplanted ovary grafts can function for many years.

CONCLUSION

We report the first successful ovary tissue allotransplant from a nonidentical sister to a Turner syndrome female requiring immunosuppression. The protocol employed for immunosuppression may turn out to be safe enough to be used liberally for nonlife saving procedures such as for ovary or uterine transplantation. The fact that ABO incompatibility did not cause rejection suggests that an ovary tissue graft may survive long-term on diffusion alone even if there is no neovascularization. The spontaneous normal pregnancy of a healthy infant girl demonstrates the benefit of an orthotopic position for the graft. The benefits of allotransplantation over donor egg IVF include the ability to conceive naturally, and also normal hormone function obviates the need for HRT.

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CRediT Authorship Contribution Statement

Sherman J. Silber: Writing – original draft, Conceptualization. **Sierra Goldsmith:** Writing – review & editing, Writing – original draft. **Benjamin Rubinoff:** Supervision, Investigation. **Eduardo Kelly:** Resources. **Rowena Delos Santos:** Supervision, Investigation. **Anibal Melo:** Supervision, Investigation. **Daniel Brennan:** Supervision, Investigation.

Declaration of Interests

S.J.S. has nothing to disclose. S.G. has nothing to disclose. B.R. has nothing to disclose. E.K. reports consulting fees from Silber Infertility Center of St. Louis as Embryology Laboratory Director. R.D.S. reports funding from Veloxis and CareDx, outside the submitted work; royalties from UpToDate, content writer; honoraria from National Kidney Foundation, symposium; leadership position, Transplant nephrology fellowship training accreditation program; and stocks in Pfizer. A.M. has nothing to disclose. D.B. reports royalties from UpToDate, Editor in Chief and Transplantation, Deputy Editor; and consulting fees from Sanofi.

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Primer alotrasplante de corteza ovárica con éxito en una paciente con síndrome de Turner requiriendo inmunosupresión: amplias implicaciones.

Objetivo: Determinar si es seguro y factible el alotrasplante de tejido ovárico de una donante no idéntica a su hermana con síndrome de Turner.

Diseño: El trasplante de tejido ovárico criopreservado, así como de tejido ovárico fresco entre gemelas idénticas está bien establecido, con informes de numerosos casos con éxito. Sin embargo, no ha habido ningún trasplante de ovario entre mujeres no idénticas, requiriendo inmunosupresión (alotrasplante ovárico). Ésta podría ser una indicación mucho más común para trasplante de tejido ovárico si existiese inmunosupresión segura y fiable.

Marco: Infertility Center of St. Louis.

Paciente: Mujer de 20 años amenorreica con síndrome de Turner 45-XO no mosaico que solicitó un trasplante de tejido ovárico de su hermana fértil de 22 años y 46-XX. Eran compatibles para el sistema de antígenos leucocitarios humanos (HLA), pero incompatibles según grupo sanguíneo AB0, una conocida contraindicación para trasplante de tejidos sólidos u órganos. La hermana con síndrome de Turner tenía una fuerte preferencia por ser capaz de obtener un embarazo de manera natural, sin utilizar ovodonación y evitando suplementación hormonal. En su comunidad religiosa esto también era importante a la hora de encontrar pareja. A pesar del pobre pronóstico asociado a la incompatibilidad AB0, se le trasplantó un ovario de su hermana fértil no idéntica de 22 años, utilizando el protocolo de inmunosupresión aplicado actualmente para trasplante renal en nuestros centros de la universidad de Washington y en Johns Hopkins.

Intervención: No aplica.

Principal medida de resultado: 5 meses tras la operación la paciente desarrolló función ovárica menstrual mensual normal y quedó embarazada espontáneamente de una niña normal. La relación entre sus niveles postoperatorios de hormona folículo-estimulante y hormona antimülleriana continúan apoyando la teoría de que la presión del tejido controla el reclutamiento de folículos primordiales. El hecho de que la incompatibilidad AB0 no haya evitado el éxito sugiere que la difusión, y no la revascularización, puede ser suficiente para la supervivencia a largo plazo de un trasplante de corteza ovárica con embarazo espontáneo.

Resultados: El alotrasplante de ovario con inmunosupresión segura permite la concepción natural, mientras que la función hormonal normal elimina la necesidad de suplementación hormonal. La colocación ortotópica del trasplante y la técnica quirúrgica son críticas para la concepción natural y una mayor tasa de embarazo.

Conclusión: El alotrasplante que requiere inmunosupresión segura, si es satisfactorio, podría ser una indicación mucho más común para el trasplante ovárico en el futuro, por encima de trasplantes de tejido criopreservado o trasplantes entre gemelas idénticas.