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Applicability of biological fertility indicators for effective birth control after orthotopic liver transplantation

Lessons learned from a single case report

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SUPPLEMENTAL BACKGROUND INFORMATION

Fertility considerations after transplantation

Progress achieved in transplantation medicine has made previously incurable diseases curable. Moreover, restoration of organ function after transplantation opens the possibility of full integration into normal life. Fertility compromised by renal or hepatic insufficiency is usually restored and maintained in young female transplant recipients shortly after surgery (Cundy et al., 1990, Coscia et al., 2015). Procreation ability and success has been recognized as a substantial factor contributing to the patient's quality of life after organ transplantation (Burra and De Bona, 2007), reflecting that parenthood is key to human realization and happiness. There is consensus that pregnancy should be avoided during the immediate post-transplantation period for at least 12 months (McKay et al., 2005, Deshpande et al., 2013, AISF, 2016). This contraindication reflects the need for graft and patient overall clinical stabilization, the recovery from subjacent disease as well as from surgical intervention and for immunosuppressant minimization, rather than the physiological achievability of pregnancy. Time to conception inversely correlates with successful and complication-free obstetric, neonatal and transplantation outcomes (Coscia et al., 2015). The above-mentioned reasons lead most guidelines to make both pregnancy avoidance recommendation as well as evidence-based recommendations for post-transplant pregnancy suitability assessment.

General criteria for the recommendation of post-transplant contraception

In 2016, the Center for Disease Control and Prevention (CDC) has issued the latest risk assessment associated to pregnancy in the two years post-transplantation (Curtis et al., 2016). Guidelines consistently contraindicate pregnancy for not less than one year post-transplantation, and they release from that contraindication after a rigorous clinical evaluation that meet strict and clear conditions to be discussed further down (AISF, 2016, Curtis et al., 2016, Deshpande at al., 2013, McKay et al., 2005). Therefore, fertility counselling is mandatory immediately after transplant and the recommendation of responsible use of reliable birth control is needed, whose length differ depending on the patient's post-transplant evolution. Even so, the choice of a method is not exempt from difficulty.

When it comes to make a recommendation, only unreliable barrier methods as well as emergency contraception are recognised as category 1 methods, i.e. a ***"condition for which there is no restriction for use of the contraceptive method"*** (Deshpande et al., 2013). The reason for this rating clearly is based on the lack of specific method-associated safety concerns, rather than for its reliability as contraceptive methods. Indeed, the recommendation as *"a valid option"* expressed by some guidelines (AISF, 2016) cannot be evidence-based defended as an effective option because of their unacceptably high typical-use failure rates of 15-30% and modest perfect use efficacies, ranging from 2-5% in general population (Trussell, 2011).

None of the most reliable methods can be rated in transplanted patients as CDC category 1. Best case, they fall into category 2 methods, in which ***"the advantages of using the method generally outweigh the theoretical or proven risk"*** (Deshpande et al., 2013). If the patient shows a complicated transplantational condition, however, methods may rapidly turn into category 3 where ***"theoretical or proven risks usually overweigh the advantages of using the method"*** or even into category 4, where the ***"condition represents an unacceptable risk if the method is used"*** (Deshpande et al., 2013). At the latest when it comes to these kinds of clinical situations, which unfortunately are not exceptional, Drs. must admit that most of the commonly used contraceptives are not universally and unrestrictedly applicable or recommendable due to its inherent nature and the transplanted patient's conditions. Therefore, the method to be proposed to each single patient should be carefully balanced during fertility counselling according on grounds of individual medical, safety and patient-derived conditions (Hilger et al., 2018). If we admit, as we find in every transplantation guideline, that even in the best case of an early uncomplicated post-transplantation evolution a pregnancy is a serious threat for the patient, the rating as a category 2 only means that the advantages overweigh risks. Advantages overweighting risks, where risks are balanced against objective and serious threats, obviously does not preclude from potential serious risks associated of category 2 contraceptives, something that authors even postulate applicable for general population (Curtis et al., 2016, Hilger et al., 2018). Consequently, the availability of a reliable category 1 method would be especially attractive for transplanted patients, as there is an unmet need for both safer and efficacious alternatives to broadly used contraceptives in transplanted patients.

Risk to benefit considerations contraceptives in transplanted patients

When considering the most efficacious methods, **surgical sterilization** is by its nature irreversible and therefore not recommendable for women with future motherhood wish. **Barrier methods**, as previously argued, are not fulfilling the needs because of poor reliability (Trussell, 2011).

Intrauterine devices (IUD) are rated as category 2 contraceptives in uncomplicated patients, or short term in complicated patient. Long-term use in patients with transplantational complications turn into category 3 and therefore continuous use might be discouraged (Deshpande et al., 2013). Specific disadvantages are infections, pathological uterine bleeding and perforation and increases in the risk of ectopic pregnancies (Trussell, 2011). In addition, they may be ethically unacceptable for users due to its abortive nature. Finally, in transplanted patients immunosuppressants have been described to reduce IUD's efficacy (Deshpande et al., 2013).

It is well known that **estrogen-based hormonal anovulatory contraceptives** have a critical safety profile in patients with cardiovascular and cerebrovascular risk factors (Hilger, 2018) They are rated as CDC category 2 contraceptives in transplanted patients with an uncomplicated evolution. They fall into category 4 as soon as patients show post-transplant hypertension, poor liver function, cardiovascular risk factors, predisposition to deep vein thrombosis (Deshpande et al., 2013). Some of these contraindications are applicable even for general population but their prevalence is increased in transplanted patients (Madhwal et al., 2012, Al Nasser et al., 2016). Other relative to absolute contraindications applicable to the general population (diabetes, smoking habits, age over 35) may further increase the patients' health risk if used indiscriminately (Curtis et al., 2016). In addition, these drugs are hepatotoxic (Srikanth and Manisee, 2013) and may therefore have consequent deleterious effect on the hepatic graft, especially if combined with immunological, infectious or isquemic complications early after engraftment. Finally, estrogenic drugs have non-negligible drug-to-drug interaction potential. Therefore, liver transplant recipients taking estrogen-based contraceptives could be exposed to a significant threat both short and long-term. This is the reason why our unit (like many others) usually contraindicates such drugs for at least 12 months post-transplantation and if we indicate them, then only in recipients with more than 6 months graft stability and in absence of other general contraindications (Coscia et al., 2015). **Progestin-only-based alternatives** are rated as CDC category 2 contraceptives with less contraindications in both complicated and uncomplicated patients (Deshpande *et al.*, 2013) but they are also prone of adverse events and they are less effective than estrogenic preparations (Trussell, 2011).

In order to avoid pregnancy, some **methods based on biological fertility indicators** (BFI) of the female cycle that helps identifying the clinical fertility window (CFW) have the best possible efficacy to side effect ratio in general population (Peragallo Urrutia, 2018). Accordingly, CDC has recently updated their evidence-based recommendation recognising that modern fertility awareness-based methods can provide practical use Pearl index between 3 and 23 in general population (Centres for Disease Control and Prevention, 2019). It being true that some of these methods can be recommended in general population to couples willing to comply with its rules as a highly efficacious method, their use hasn't been documented in medical literature for transplant recipients. Therefore, they cannot be assigned to a CDC category based on evidence. Guidelines do not consider them for this reason (McKay et al., 2005, Deshpande et al., 2013, Coscia et al., 2015), except Italian guideline that dismiss their usefulness (AISF, 2016) supporting their statement by a reference that neither speaks about fertility-awareness methods in transplantation nor provides any kind of evidence.

In the general population, the **symptothermal method (STM)** has shown methodological failure rates as low as 0.2-0.8% (Rötzer, 1968, European-NFP-Study-Groups, 1993, Frank-Herrmann et al., 1997, Fehring et al. 2008), with an overall Pearl Index ranging from 0.8-3.6%, comparable to that of modern combination anovulatory drugs (Peragallo Urrutia, 2018, Trussell, 2011). However, for reliable application, good instruction, follow-up, and special motivation for responsible application is needed.

Single BFI-based methods have worse overall efficacy rates as compared with combined BFI methods. Cervical mucus-based methods are less likely to have method-failures during the pre-CFW (Arévalo, 2004, Bhargava, 1996, Howard and Stanford, 1999). By contrast, temperature-based methods have been shown unbeatable for pregnancy avoidance once post-ovulatory infertility period is set (Döring, 1967). STM method profits from these complementary strengths of single-BFI methods for pregnancy avoidance.

SUPPLEMENTAL METHODS

Development of hepatopathy and transplantation

On September 2011, after her first complication-free pregnancy, a 31-year old Caucasian female carried out a healthy male offspring at postmenstrual week 41 by caesarean section. Patient had normal gyneco-obstetric anamnesis. Initial puerperium was normal and mother breastfed upon demand, with partial infant formula supplementation. At approximately day 10 postpartum woman referred abdominal pain and was ambulatory-treated symptomatically after excluding puerperal complications by echography. As pain increased and symptomatology worsened with the appearance of jaundice, hyperbilirubinemia and hypertransaminasemia, she was admitted to hospital on October 9th. Patient did not take hepatotoxics. Pathological findings of the explanted liver showed massive necrosis with overall parenchymal loss. The ethiology of infarcts could not been identified and was diagnosed fulminant idiopathic hepatic failure. Four days post-admission patient had to be intubated after progressive worsening of general condition and hepatic insufficiency with severe coagulopathy and grade III encephalopathy. MARS treatment was initiated, and patient listed for urgent liver transplantation, which happened two days later, on October 15th.

The graft was from a multiorgan brain death donor and had at reperfusion a cold ischemia time of 4:50 hours. Both donor and patient were CMV positive. No antiviral prophylaxis was indicated. After surgery, patient had immediate graft function leading to hepatic values normalization within the first 12 days post-transplantation. The only meaningful complication was a right side intraparenchimal brain hematoma associated to the ICP sensor which resolved without meaningful complications, and a mild cholestasis episode probably associated to a non-biopsy proven acute rejection, which resolved without need of immunosuppression changes. The patient was discharged home at day 28 post-transplantation, and followed up according to local practice.

Immunosuppressive therapy was based on basiliximab induction and tacrolimus and mycophenolate mofetil (MMF) maintenance. Initial tacrolimus target levels of 10-11 ng/ml were continuously tapered to 6-7 ng/ml within month 6 post-transplantation. Fix dose of MMF of 1 g b.i.d. was maintained until January 2012, time at which it was reduced to 250 mg b.i.d. due to appearance of neutropenia and anaemia.

Further evolution was without meaningful events except a CMV reactivation on December 2012, which was successfully treated with a 2 week-course of oral Valgancyclovir. The patient remained normotensive, normoglycemic, with stable graft and renal function, rejection and infection free.

Training and application of symptothermal method

The couple received training for STM from one of our experienced physicians, following our standard STM protocol (Soler et al. 1995). Patient had follow-up by regular visits to our centre and phone-calls when necessary. STM is based on recognition of at least 2 BFIs in both pre and post-ovulatory phases. The couple was counselled to avoid marital intercourse during the CFW.

For basal body temperature measurement woman used a clinical Gallium-column-thermometer. During the first cycle, a backup thermometer was calibrated with the principal one. Body wake-up temperature values were transferred to a paper-based STM record and interpreted as previously described for general population using the 3 over 6 rule or their described two exceptions (Rötzer, 1968).

The patient was trained and asked to identify across the menstrual cycle for absence or presence of cervical mucus and/or vaginal moisture sensation, as well as for the evaluation of physicochemical properties of cervical mucus. These data were transferred to the STM chart. Appearance of cervical mucus of any consistency or moisture sensation was always presumed as a sign of fertility from the beginning of the menstrual cycle until diagnosis of postovulatory infertility (Rötzer, 1968). Peak day was defined as the last day in which cervical mucus showed the qualitatively most fertile characteristics.

Cervical mucus evaluation was accompanied by cervical auto-examination. We decided to train our patient to determine the characteristic cervix uteri changes as a complementary, accessory variable for the CFW determination (Insler et al., 1972). The patient's previous delivery having been by caesarean section facilitated this task, as cervix remained unaffected.

According to the well-known STM rules (Frank-Herrmann et al., 1997), fertility was assumed to have started at day 6 of each menstrual cycle with a preceding cycle showing a biphasic temperature pattern, or when the presence of cervical secretion could be felt or observed by the woman, whichever occurred first. End of CFW was assumed when both a temperature raises of at least 3 days occurred and 3 days after the cervical mucus peak day could be assessed by the woman (Frank-Herrmann et al., 1997).

In the present case, no calculation rules could be applied because this would have required a minimum of 12 cycles of observation after delivery or transplantation. On the other hand, the *minus-20-rule* (Rötzer, 1968) could be used after second delivery after 12 cycles of observation, allowing a significant length reduction of presumed CFW.

SUPPLEMENTAL RESULTS

Identification of biological fertility indicators and application during post-transplantation period

At time of first presentation at our family orientation unit lactation had already been discontinued, but amenorrhea persisted until week 29 postpartum (23 post-transplantation). After her first menses, patient was followed for 13 cycles (19 months post-transplantation). The couple was able to identify and evaluate all BFI and acquired full autonomy in diagnosing CFW before their third cycle of observation, a time at which graphs were only checked for confirmatory purposes and filing.

Evaluation of fertility indicators

Despite having experience in teaching STM, including during puerperal phase, in this case our team was confronted with specific challenges. Besides helping the couple to screen, detect and measure BFI, the impact of the hepatic allograft and multiple medications on BFI was assessed without the help of literature describing applicability of BFI for CFW identification after transplantation. After surpassing the recommended pregnancy-free time, the challenge was to identify best moment for the patient's intended new pregnancy. The couple strictly followed STM rules, which initially restricted their sexual activity to the post-ovulatory infertility period in double control, confirmed by cervical evaluation.

End of amenorrhea at week 29 was preceded by an ovulation, as evidenced by the characteristic biphasic pattern of observed basal body temperature, wherefore a true menstruation could be assumed (Döring, 1963). After that, the patient was followed for 12 consecutive cycles, the complete period in which a pregnancy was contraindicated by her transplant physician. Statistics of those cycles are shown in Table 1.

Basal body temperature

The couple had no problem in correctly identifying temperature raises from the first cycle onwards. Despite being ovulatory, the first cycle was retrospectively identified as likely infertile because of luteal insufficiency, evidenced by only 9 days of post-ovulatory raised temperature (Döring, 1969). Likewise, all following cycles were assessed as ovulatory, as they showed the characteristic biphasic pattern. Overall, luteal phase was within the limits of normality with only 1 out of the 12 follow-up cycles showing luteal insufficient, as defined by less than 10 increased postovulatory temperatures. Indeed, in the 13th cycle, intended pregnancy was achieved and maintained without progestin supplementation, confirming corpus luteum sufficiency.

Even though the MMF used in her immunosuppressive regimen is known to increase basal body temperature (European-Medicines-Agency, 1996), a characteristic biphasic temperature curve was detectable at the end of the puerperal cycle, showing that ovulation took place just before the end of amenorrhea and in every follow up cycle. Therefore, MMF did not preclude from identifying biphasic temperature curves nor did it affect the STM interpretation rules.

Cervical Mucus

The patient correctly identified cervical secretion across her cycle; she was able to differentiate and correctly interpret her mucus patterns according to STM rules. During her first cycle (puerperal phase), she recorded 4 patches of mucus and identified 4 peaks of mucus. The last peak correlated with the temperature rise that diagnosed first ovulation. Afterwards, all 13 follow-up cycles showed one single characteristic mucus course, all correlating with a temperature raise. The patient became confident and autonomous in the identification of mucus-based CFW as expected, within the first couple of months.

Cervix uteri

The patient was able to start self-exploring her cervix uteri from the beginning of her learning process and reported to correctly identify the expected changes. Data from cervical self-exploration showed temporal consistency with the information from cervical mucus observation. This consistency contributed to the user's confidence in the correct identification of their CFW.

Post-transplantation obstetric follow-up and neonatal outcome

Fourteen months post-transplantation, the couple manifested their interest in becoming pregnant again. At that moment, CMV reactivation was diagnosed as the reason for which the patient was counselled to wait. Five months later, without having experienced active CMV infection and with the patient's clinical condition remaining stable, pregnancy was no longer contraindicated. Due to its teratogenic potential MMF was discontinued 6 weeks before release from pregnancy contraindication (European-Medicines-Agency, 1996). Figure 2 shows a possible recommendation for pregestational evaluation of a transplanted woman, based on the recommendations of the American Society of Transplantation (McKay et al., 2005) and Spanish Clinical Guidelines for the follow-up of pregnancy and puerperium (Spanish Ministry of Health, 2018)

Finally, pregnancy was achieved during the first cycle of attempt. From that time point onwards the patient was carefully monitored at her transplantation hospital by a multidisciplinary team composed of liver-transplant physicians and obstetricians of the high-risk pregnancy unit.

The patient experienced an episode of acute rejection right after conception, which was successfully treated with methyl-prednisone boluses. Corticotherapy was tapered down to a dose of 20 mg, which was continued for the rest of the pregnancy. Her evolution was without any other event, with normal and stable graft function, without gestational diabetes and normotensive.

The patient experienced premature rupture of membranes and gave birth by vacuum-assisted vaginal delivery to a 35+6 week-old, 2.5 kg heavy healthy girl. Initially baby developed hyperbillirubinemia, successfully treated by phototherapy, without further neonatal complications to be reported. Maternal lactation being contraindicated, the baby was fed with neonatal formula and showed a satisfying paediatric evolution.

After delivery, MMF was reintroduced at a dose of 1 g b.i.d. and corticosteroids tapered until discontinuation. Immunosuppression has been maintained without changes since then. Patient's hepatic allograft stood stable without any hospital admission or meaningful medical event.

Afterwards, the patient continued with determination of CFW using her well-known BFI. After the end of amenorrhea her cycles were ovulatory, normal in length, showing spotting around ovulation and without luteal insufficiency. The couple was sexually active, following the STM rules and successfully avoiding a further pregnancy for now more than 6 consecutive years.

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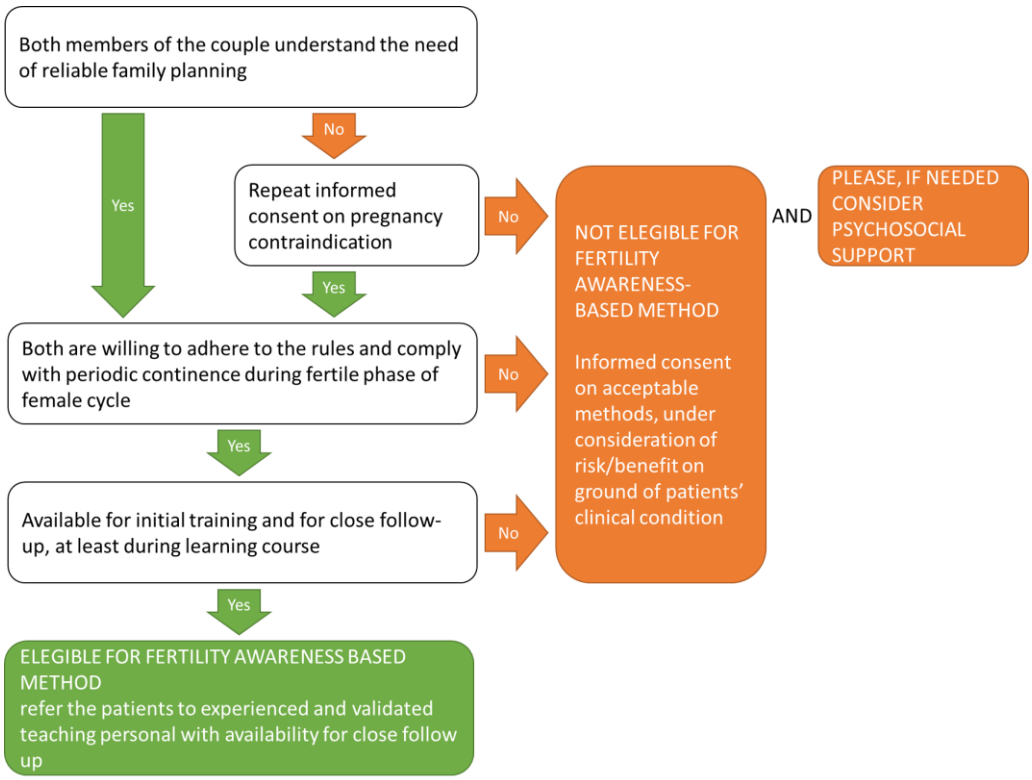
RECOMMENDED OF DECISION MAKING ALGORYTHM

Figure 1: Eligibility for use of Fertility awareness-based methods



Pre-obstetrical counselling