

# Assisted reproductive technology

## What is needed in the Kingdom of Saudi Arabia?

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### ABSTRACT

In 1978, the first in vitro fertilization baby was born. Since then, we have seen the introduction of several new modalities of assisted reproductive technologies (ART), and the spread of ART procedures throughout the world. The number of ART units in the Kingdom of Saudi Arabia is increasing rapidly. The associated complications of ART procedures include fetal, maternal and childhood.

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In 1968, the late Dr. Patrick Steptoe was able to retrieve a mature oocyte from the ovary in a human female for the first time.<sup>1</sup> Although egg retrieval has been accomplished in animal several decades earlier, 1968 marked the beginning of human in vitro fertilization (IVF).<sup>2</sup> Following this, a race similar to the space program race decades earlier was started between 3 sub-continent (Europe, America and Australia) to produce the first IVF baby. Ten years later, on 25th July 1978, Louise Brown, was born using IVF treatment in a small town in England called Oldham, following collaboration between the late Steptoe and Edwards.<sup>3</sup> Since then, assisted reproductive technology (ART) units have sprung up throughout the world, and new techniques are introduced every few years. Great improvements have taken place in the culture media used for the embryo, and more recently and ambitiously the pre-implantation diagnosis, particularly with the major advances in the human genome project. This remarkable advancement in science and medicine has brought happiness and continues to do so for a large number of infertile couples who thought they would never be able to become parents.

Infertility, prevalence and causes. Infertility affects 10-12% of married couple's worldwide.<sup>4</sup> It is defined by the inability of the woman to conceive after 1-2 years of unprotected sexual intercourse without any obvious cause for their infertility.<sup>4,5</sup> All experts in the field of infertility feel that a couple should be referred for counseling after one year of unprotected intercourse if the woman fails to conceive. The question of whether to start treatment after one or 2 years of infertility continues to be a matter of debate. The causes of infertility in general accounts for one third being due to male factors (hypospermia, aspermia, endocrine factors and others) and 50% are due to female causes (ovarian, tubal, uterine, unexplained and others), whereas 10-15% remain unexplained.<sup>4,6</sup> An inverse relationship exists between the age of the female and fertility. Women at the age of 30 years have a 70% chance of conceiving while women of 44 years or more have only 14% chance of conceiving. This factor is very important because the current trend is for some women to attempt conception at 35 years of age or later following the

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establishment of their professional career. In men, the testosterone level decreases and gonadotrophin level increases with age.<sup>7</sup> This could lead to a decrease in sperm count and quality.

Assisted reproductive technology. Although IVF was the first technique to be employed, but only following introduction of other types of gametes handling, the term ART was commonly used. There are several types of ART.

***In vitro fertilization (IVF).*** This technique was the first to be utilized in 1978 by Steptoe and Edward.<sup>3</sup> The ovum was placed back in the uterus after fertilization through the cervix.

***Gamete intra fallopian transfer (GIFT).*** This technique was introduced in 1984. Both ovum and the sperm are put back into the fallopian tube before fertilization by a laparoscope through an abdominal incision.<sup>8</sup>

***Zygote intra fallopian transfer (ZIFT).*** This was introduced in 1986 in which the fertilized egg is placed back into the fallopian tube through a laparoscope. There are several subtypes of ZIFT depending on the stage of the zygote when the transfer takes place, such as, tubal embryo transfer (TET).<sup>9</sup>

***Intracytoplasmic sperm injection (ICSI).*** This procedure was introduced first in Belgium in 1992, in which a single sperm is needed to fertilize the ovum. The ICSI has revolutionized the treatment of male infertility.<sup>10</sup>

Other new modalities of ART have been introduced such as assisted hatching and blastocyte transfer.

Treatment of infertility. Ovulation induction alone or in preparation for ART cycle, one of the ART procedures is utilized or a combination of more than one can be used at any given cycle, non-ART procedures such as intra-uterine insemination (IUI), embryo donation, surrogacy, cryopreservation of sperm and embryo and combination of more than one of the above mentioned methods. Maternal age, the various causes of infertility, the number of embryos transferred in each cycle, cryopreservation and improvement in endometrial receptivity, could all affect the success rate of ART.

***Complications of ART.*** The complications of the ART include fetal, maternal<sup>11,12</sup> and neonatal (Table 1). Although the frequency of adverse neonatal outcome is still debatable, large population studies suggest significantly increased risk for adverse neonatal outcome.<sup>13-17</sup> This adverse neonatal outcome could be due to one or more of the following factors: Prematurity and its complications, relatively advanced age of the infertile couple, the underlying cause of the infertility and factors associated with the ART procedures themselves. The medication

used to induce ovulation or to maintain pregnancy and the ART procedures themselves could affect the embryo, fetus and even children later in life, such as imprinting disorders and childhood cancer.<sup>17,18</sup> In most European countries, USA, Canada, Australia and many other countries legislation and guidelines have been formulated in order to reduce the risk of both maternal and neonatal complications. The latest comprehensive guidelines were published by the National Institute for Clinical Excellence (NICE) UK, February 2004.<sup>19</sup> The guidelines deal with the various aspects of ART (medical, ethical and social). With regards to the patient, it emphasizes the right of the patients to make an informed decision with regard to the type of procedure, the risk of maternal and infant complications and the cost involved. This is carried out by counseling the couples by personnel who are not directly involved in the ART procedure. Verbal, written, audiovisual and internet sites have been offered. Psychological, social as well as financial supports are included.

The situation in the Kingdom of Saudi Arabia. ***Availability of ART.*** In the Kingdom of Saudi Arabia, ART was introduced long time ago. In the capital, Riyadh, there are currently at least 12 ART units, in the Kingdom's second largest city, Jeddah, there are more than this. When compared to Western Australia, with a population of 2 million there are only 3 private units providing ART.<sup>15</sup> There are also ART units in the other major cities of the Kingdom. In addition, ovulation induction drugs are prescribed in the Kingdom's governmental hospitals and private clinics, and can even be bought by the general public over the counter.

***The availability of the neonatal intensive care (NICU) beds.*** The current practice in most ART units in the Kingdom is to transfer 2, 3, 4 or more embryos at each cycle. This practice is certain to lead to a higher incidence of multiple births. As a result, the low birth weight (LBW) and very low birth weight (VLBW) incidence rate will be higher with its associated complications.<sup>13,16</sup> In NICU at the Riyadh Armed Forces Hospital, the number of babies admitted to the NICU following ART or ovulation induction has risen and continues to rise (Figure 1). In 2004, 65 such babies were admitted to our NICU. This represents 6% of the total and 22% of the VLBW baby's admitted.<sup>20</sup> The availability of the ART service will increase the workload on all the NICUs in the Kingdom and most units are not prepared to deal with such a sudden, unplanned increase in the workload.

***Legislation and guidelines.*** Although legislation is present, it is not widely disseminated and even in some units, the medical staff are not aware of its existence. Guidelines about the various modalities of treatment, their indication and contraindication,

Table 1 - Complications of assisted reproductive technology.

<p><b>1. Early pregnancy loss</b></p> <p>a. Abortion (preclinical and clinical)</p> <p>b. Vanishing fetuses</p> <p>c. Ectopic and Heterotopic pregnancies</p> <p><b>2. Maternal complications</b></p> <p>a. Ovarian hyper stimulation syndrome which could be fatal.</p> <p>b. Ovarian cyst formation</p> <p>c. Ovarian cancer</p> <p><b>3. Neonatal adverse outcome</b></p> <p>a. Multiple births:</p> <p>    Twin 25%</p> <p>    Triplet 6%</p> <p>    Higher rate &gt;0.6%</p> <p>b. Higher incidence of low birth weight and very low birth weight babies</p> <p>c. Higher incidence of cerebral palsy and mental retardation.</p> <p>d. Congenital malformation.</p> <p>e. Chromosomal anomalies.</p>
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their success rates and the risk involved with each procedure, are not available. More importantly, there are no guidelines for the infertile couples in any form from an independent organization within the Kingdom.

What is needed in the Kingdom of Saudi Arabia? The legislation already in place may need to be updated, disseminated, and enforced. There should be an accountability of all these units to the authority and to their clients. Doctors who prescribe ovulation induction drugs and medical staff at ART units should know when and where the woman will deliver, should she become pregnant. There should be a registry of all ART cycles indicating whether they were completed or canceled, in order to assess the efficacy of treatment and to monitor outcome. An independent body would need to be established, such as NICE in the UK, with a similar structure to produce evidence-based guidelines to be followed for various medical problems, including ART. This body also can advise parents on the nature of the various ART procedures, the rate of success for each procedure and the risks involved. Guidelines with regard to the process of advertisement for ART needs to be established using the American Society for Reproductive Medicine and NICE as a model.<sup>21</sup> The number of eggs transferred in each cycle should be considered seriously. In most European countries, it does not exceed 2 eggs in all the circumstances. Currently in some Scandinavian countries, only one or 2 fertilized egg are transferred back with good pregnancy rates.<sup>22-25</sup> With the improvement in the technique of cryopreservation, it has been shown that repeated cycles with single embryo transfer carry a better success rate than with multiple embryo transfers.<sup>25,26</sup> In addition, single embryo transfer will eliminate triplet and higher order multiple pregnancies and it is cost effective even if a repeated cycle is

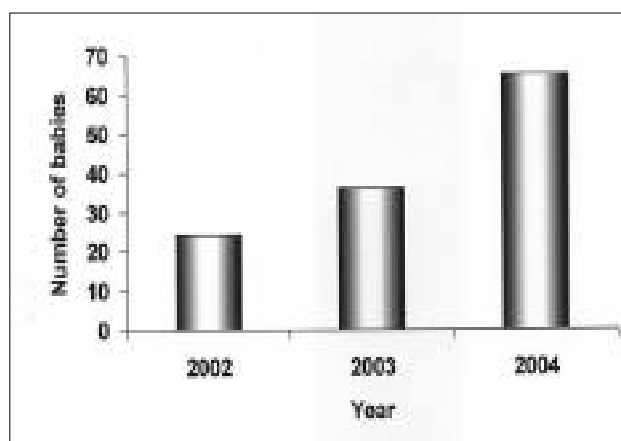


Figure 1 - Number of babies admitted to the neonatal intensive care unit following the assisted reproductive technology and ovulation induction.

needed to achieve the same success rate as with multiple embryo transfer.<sup>25-27</sup> Most infertile couples need social, psychological and possibly financial support before, during and after they have gone through the treatment cycle, whether the cycle is subsequently successful or not.<sup>5</sup> Babies born after ART need to be monitored because in addition to the higher rate of cerebral palsy<sup>14</sup> and other birth defects,<sup>15,17</sup> there are a few disturbing reports which showed a higher incidence of imprinting disorders such as Beckwith-Wiedemann Syndrome<sup>28,29</sup> and childhood cancer.<sup>30-32</sup>

## References

1. Steptoe PC. Laparoscopy and Ovulation. *Lancet* 1968; 7574: 913.
2. Chang MC. Fertilization of rabbit ova in vitro. *Nature* 1959; 184: 466-467.
3. Steptoe PC, Edwards RC. Birth after the reimplantation of a human embryo. *Lancet* 1978; 2: 366-377.
4. World Health Organization. Infertility: A Tabulation of available data on prevalence of primary and secondary infertility. WHO programmed on maternal and child health and family planning, division of family health. Geneva: WHO; 1991.
5. National Institute Clinical for Excellence. Scope: Assessment and treatment for people with Fertility problems, 2002. Available from URL: <http://www.nice.org.uk>
6. Reproductive Health Outlook (RHO). Overview and lessons learned. Infertility. Available from URL: <http://www.rho.org/infertility/overview/html>
7. Guyton AC, editor. Reproductive and hormonal functions of the male. Text book of Medical Physiology. 7th ed. Philadelphia: W.B. Saunders Company; 1986. p. 954-967.
8. Asch RH, Ellsworth LR, Balmaceda JP, Wong PC. Pregnancy after translaparoscopic gamete intrafallopian transfer. *Lancet* 1984; 2: 1034-1035.
9. Devroey P, Braeckmans P, Smits J, Van Waesberghe L, Wisanto A, Van Steirteghem A, et al. Pregnancy after translaparoscopic zygote Intrafallopian transfer in a patient with sperm antibodies. *Lancet* 1986; 8493: 1329.

10. Palermo G, Joris H, Devroey P, Van Steirteghem AC. Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. *Lancet* 1992; 340: 17-18.
11. Rossing MA, Tang MT, Flagg EW, Weiss LK, Wicklund KG. A case-control study of ovarian cancer in relation to infertility and the use of ovulation-inducing drugs. *Am J Epidemiol* 2004; 160: 1070-1078.
12. Fuller PN. Malignant melanoma of the ovary and exposure to clomiphene citrate: a case report and review of the literature. *Am J Obstet Gynecol* 1999; 180 (6 Pt 1): 1499-1503.
13. Schieve LA, Meikle SF, Ferre C, Peterson HB, Jeng G, Wilcor LS. Low and very low birth weight in infants conceived with the use of assisted reproductive technology. *N Engl J Med* 2002; 346: 731-737.
14. Stromberg B, Dahlquist G, Ericson A, Finnstrom O, Koster M, Stjernqvist K. Neurological sequelae in children born after in-vitro fertilization: a Population-based study. *Lancet* 2002; 359: 461-465.
15. Hansen M, Kurinczuk JJ, Bower C, Webb S. The risk of major birth defects after intracytoplasmic sperm injection and in vitro fertilization. *N Engl J Med* 2002; 346: 725-730.
16. Schieve LA, Ferre C, Peterson HB, Macaluso M, Reynolds MA, Wright VC. Perinatal outcome among singleton infants conceived through assisted reproductive technology in the United States. *Obstet Gynecol* 2004; 103: 1144-1153.
17. Kurinczuk JJ, Hansen M, Bower C. The risk of birth defects in children born after assisted reproductive technologies. *Curr Opin Obstet Gynecol* 2004; 16: 201-209.
18. Schieve LA, Rasmussen SA, Buck GM, Schendel DE, Reynolds MA, Wright VC. Are children born after assisted reproductive technology at increased risk for adverse health outcomes? *Obstet Gynecol* 2004; 103: 1154-1163.
19. National Institute for Health and Clinical Excellence (NICE). Fertility: assessment and treatment for people with fertility problems. Available from URL: <http://www.nice.org.uk>
20. Riyadh Al-Kharj Hospital Programmed. Neonatal Intensive Care Unite, Annual Report. Riyadh (KSA): Riyadh Armed Forces Hospital; 2004.
21. Practice Committee, Society for Assisted Reproductive Technology and the American Society for Reproductive Medicine. Guidelines on the number of embryos transferred. *Fertil Steril* 2004; 82: 773-774.
22. Thurin A, Hausken J, Hillensjo T, Jablonowska B, Pinborg A, Strandell A, et al. Elective single-embryo transfer versus double-embryo transfer in in-vitro fertilization. *N Engl J Med* 2004; 351: 2392-2402.
23. The Practice Committee of the Society for Assisted Reproductive Technology and the American Society for Reproductive Medicine. Guidelines on the number of embryos transferred. *Fertil Steril* 2004; 82:773-774.
24. Davis OK. Elective Single-Embryo Transfer. Has its time Arrived? *N Engl J Med* 2004; 351: 2440-2442.
25. Templeton A, Morris JK. Reducing the risk of multiple births by transfer of two embryos after in vitro fertilization. *N Engl J Med* 1998; 339: 573-577.
26. Vilksa S, Tiitinen A, Hyden-Granskog C, Hovatta O. Elective transfer of one embryo result in an acceptable pregnancy rate and eliminate the risk of multiple birth. *Human Reprod* 1999; 14: 2392-2395.
27. Lukassen HG, Schonbeck Y, Adang EM, Braat DD, Zielhuis GA, Kremer JA. Cost analysis of singleton versus twin pregnancies after in vitro fertilization. *Fertil Steril* 2004; 81: 1240-1246.
28. Chang AS, Moley KH, Wangler M, Feinberg AP, DeBaun MR. Association between Beckwith-Wiedemann syndrome and assisted reproductive technology: a case series of 19 patients. *Fertil Steril* 2005; 83: 349-354.
29. Cox GF, Burger J, Lip Va, Mau UA, Sperling K, Wu BL, et al. Intracytoplasmic sperm injection may increase the risk of imprinting defects. *Am J Hum Genet* 2002; 71: 162-164.
30. Bruinsma F, Venn A, Lancaster P, Speirs A, Healy D. Incidence of cancer in children born after in-vitro fertilization. *Hum Reprod* 2000; 15: 604-607.
31. Moll AC, Imhof SM, Cruysberg JRM, Schouten-van Meeteren AYN, Boers M, van Leeuwen FE. Incidence of retinoblastoma in children born after in-vitro fertilization. *Lancet* 2003; 361: 309-310.
32. Olshan AF, Smith J, Cook MN, Grufferman S, Pollock BH, Stram DO, et al. Hormone and fertility drug use and the risk of neuroblastoma: a report from the Children's Cancer Group and the Pediatric Oncology Group. *Am J Epidemiol* 1999; 150: 930-938.