


XVI Congreso Argentino en Medicina Reproductiva
Reunión Internacional IFFS-SAMeR 2014

Invitados Extranjeros

Tina Buchholz *Germany*

Epigenetics and Imprinting in ART (Genetics and Reproduction Trilogy)

Epigenetics describes the phenomenon of heritable variations which are not caused by the of the DNA sequence. Several mechanisms have been elucidated including DNA methylation, histone modification and some more. Genomic imprinting leads to differential parental expression of genes and therefore to parental specific inheritance. Some diseases have been identified to be depending on genomic imprinting.

Both genetic phenomenon will be explained in the lecture and on the relation to human reproduction will be focused. Inheritance of epigenetic alterations had been in the spotlight as modifications due to environmental changes. It has become more and more elucidated that these factors can influence health related issues in following generations. Specific concerns have been raised about the influence of culturing media in the process of ART, which falls in line with major physiological epigenetic changes during the first few days of embryonic development.

Implantation failure (Embryo Biomarkers & Quality Trilogy)

Implantation is a highly complexprocess, which needs a balance of immunological, hemostaseological, geneticalend endocrinologicalfactors. If one of those fails, implantation failure can occur in spontaneous conceived pregnancies recurrently aswell as in pregnancies following ART.

This presentation will explain the current understanding of those mechanisms as well as the up to date treatment options. Most of which are still highly controversial and stringent explanations for recurrent implantation failure are still to be elucidated. The presentation includes the embryonic as well as the endometrial perspective and the interaction of the both players.

Basil C. Tarlatzis *Greece*

Does progesterone elevation affect pregnancy outcome after IVF?

The role of progesterone levels on the day of human chorionic administration in the context of stimulated cycles co-treated with GnRH analogues has been a matter of intense debate for over two decades. Today, there is convincing evidence that in the general population the presence of an elevated progesterone concentration on the day of hCG is associated with a decreased probability of pregnancy achievementafter a fresh in-vitro fertilization cycle.

The potential moderating effect of ovarian response on the latter association seems to be an important parameter when evaluating the clinical implications of progesterone elevation.

Several studies have attempted to evaluate the effect of progesterone elevation on the cycle outcome of hyper or hypo responders, thus testing the hypothesis that the effect of progesterone elevation on the probability of pregnancy might be indeed dependent on the type of ovarian response.

Although the available evidence is limited, there are strong indications that in hypo responders the effect of progesterone elevation is even more prominent than the general population. At the same time, in hyper-responders, where progesterone elevation is more frequent, a concentration of P>1.5 ng/mL might not be sufficient to cause a clinically significant deterioration in terms of pregnancy rates. In these patients, higher concentrations of progesterone on the day of hCG are required for a decrease in pregnancy rates to be evident.

Overall, available evidence suggests that hypo-responders undergoing fresh IVF cycles are more vulnerable to the negative effects of progesterone elevation, whereas hyper-responders, who are patients of better prognosis, seem to be able to partially compensate for this effect.

These interesting findings highlight the complexity of the role progesterone elevation in fresh IVF cycle outcome and also the need for further research in this field.




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Rachel Cutting *UK*

Epigenetics and Imprinting in ART (Genetics and Reproduction Trilogy)

It is paramount to address the safe use of liquid nitrogen within an IVF laboratory as fatalities due to asphyxiation are reported every year. Liquid nitrogen when warms has an expansion ratio of 1:683, rapidly displacing oxygen from the air. It is therefore essential to consider lab design to ensure that adequate storage of vessels and laboratory ventilation are provided. Other aspects to consider are how liquid nitrogen is accessed, what type of alarm systems are used for low oxygen in the lab and low levels of nitrogen in the dewars, and the correct use of personal protective equipment. As well as staff safety all samples must be stored in a safe environment. Consideration should be taken to minimise the risk to samples in the event of a vessel failure, and that of sample-sample viral transmission (the UK policy for screening patients will be discussed).

Comprehensive risk assessments should be undertaken to ensure no harm comes to either stored samples or staff.

Training in ART: Clinical Laboratory

Effective training is essential in a successful IVF programme. Laboratory staff should be trained to a high standard to ensure reproducibility and consistency. The Association of Clinical Embryologists in the UK introduced a formal training programme in the 1990s which produced high quality embryologists. More recently the UK government has undertaken a total review of training and the Modernisation of Scientific Careers programme has lead to a national training programme for all health care scientists. Embryologists are now all trained through the Scientist Training Programme (STP) which is a 3 year masters level programme which combines practical training in a clinic and academic teaching through a university, and includes completion of a research project and dissertation. The first graduates completed this comprehensive training in 2014.

Quality Control in ART

Routinely working to a high standard with attention to detail is key to the delivery of a successful IVF programme. An overarching quality management system ensures that consistency and high standards are maintained. External and internal quality control schemes can be employed. The facility should be designed to provide a stable environment with respect to air quality and temperature and critical equipment should be validated; temperature mapping of incubators is a useful exercise. Although daunting, validation is a useful tool to identify non conformances of equipment which may previously have gone undetected. It can also be a used as a management tool to justify expenditure and to formulate a business case for new equipment. Every aspect of a programme should be included within the quality management framework, which should also include staff training and competency assessment. To monitor effectiveness of the quality management system a comprehensive audit programme should be implemented.

How to improve embryo quality in the laboratory

There are many factors which can have an impact on embryo quality. Whilst the laboratory environment plays a crucial role, factors such as the stimulation regimen and patient aetiology may also affect quality and the chance of achieving a pregnancy. However, as embryologists we strive to achieve the optimal environment to minimise embryo stress which may then decrease embryo viability. Consideration of lab design, incubator type and culture medium should also be taken seriously. With respect to embryo development, changes in 3 key areas will cause stress; changes in temperature, pH and osmolarity. Staff should be trained to work efficiently to minimise variation of these factors. With the increased use of blastocyst transfers, the use of low oxygen incubators can provide a more optimal environment for the developing preimplantation embryo. Optimising the laboratory can minimise stress and maximise viability of embryos, thereby having a positive effect on live birth rates.




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Carlos Sueldo *USA / Argentina*

Infertilidad masculina

La infertilidad masculina constituye aproximadamente el 50% de todos los casos de infertilidad, solo o combinado con un factor femenino. En su evaluación, el análisis de semen ha sido una herramienta valiosa para evaluar inicialmente el potencial reproductivo del varón infértil. Las nuevas herramientas se introdujeron con el fin de mejorar su valor diagnóstico y aquellos serán revisados durante la Conferencia. El valor de las pruebas de estrés oxidativo, así como los nuevos datos en el área de la genética, también se presentará.

Impacto de los tratamientos oncológicos sobre la fertilidad

Un número importante de los cánceres se producen en pacientes de sexo femenino antes de los 40 años de edad; la mayor supervivencia y la cura de varios tipos de cáncer en los últimos decenios, crea la necesidad de preservación de la fertilidad en el enfoque terapéutico; basado en el plan prescrito para el tratamiento de estos pacientes (quimioterapia, radioterapia, cirugía), los clínicos pueden indicar los ovocitos / embriones de criopreservación como una manera muy exitosa para preservar la fertilidad; También se revisó el valor de la biopsia de tejido ovárico y criopreservación para la futura implantación.

Adjuncts to COH Protocols (Abstract)

ART has become one of the most effective infertility treatments available today; in the so-called good prognosis/good responders ART patients (both IVF and ICSI), the fresh transfer of two blastocysts in our Center generates a Clinical Pregnancy rate around 60 %, besides, as excess embryos are available for blastocyst freezing and future thawing and transfer, the overall pregnancy potential or cumulative pregnancy rate from a single cycle/attempt in this patient population is quite impressive.

There is a large number of ART patients that fall outside the scope of this good prognosis/good responders ART group, as their ovarian response to COH is either excessive or very poor; they both create clinical problems, as they either do not have enough follicles/oocytes after ovarian stimulation to justify moving forward with the treatment cycle, or they hyper-respond to the stimulation protocol administered.

The hyper-responders are easier to deal by modifying the COH protocols in various ways; on the other hand poor responders are clinically a very difficult group to treat and is here where a number of adjuncts have been suggested in order to enhance the ovarian response. The use of aspirin, Growth hormone, testosterone and DHEA as adjuncts to COH protocols in poor responders (typically microdose flare or GnRh Antagonist, in tandem with high doses of gonadotropins) have been proposed by different investigators. Their possible mechanism of action and potential benefits is going to be discussed during this presentation.




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Paul Devroey *Belgium*

New Approaches of ovarian stimulation in poor reponders

Apparently there are many definitions of poor responders. Apparently the authors of the Bologna criteria did an important step. By standardizing a common language is introduced.

Besides female age, three parameters are crucial: AFC, AMH and FSH. If all 3 are resulting into a similar conclusion, it is apparent that the stimulation will be problematic .

From a clinical standpoint rational thinking is of paramount importance. It seems as a paradox that a low AFC will and in a normal response Different strategies will be critically proposed. It seems apparent that besides the number of cumulus-oocyte-complexes their genetic components have to be taken in to account. This observation leads to the question of the role of genetic testing.

ICSI for all WHY? WHY NOT?

Icsi had been developed for the gamete treatment in case of male infertility in 1992. It became very transparent that this treatment would change the entire approach in conditions the couple was infertile due to male factor infertility.

Needless to say that azoospermia has been an important issue. In 1995 the first pregnancies were described with testicular sperm extraction. TESE has been introduced for obstructive and non-obstructive azoospermia.

The percentage of males remaining infertile remains minute.

Since ICSI became so efficient, many groups worldwide became intrigued and did apply this technology to all couples. It is almost impossible to judge if this is a wise decision.

Is there sufficient information on malformation rates ? This key question is still open.

Stratis Kolibianakis *Greece*

Overview of different types of clinical trials

Clinical trials are performed to answer a specific question. For each question, however, several types of studies are available, each of which might be more or less suitable or more or less feasible to be performed. Studies are either descriptive or analytic.

Non-analytic or descriptive studies do not try to quantify a relationship but try to give a picture of what is happening in a population, e.g., the prevalence, incidence, or experience of a group. Non-analytic or descriptive studies are usually case reports, case-series, qualitative studies or surveys (cross-sectional). These type of studies measure the frequency of several factors, and hence the size of the problem.

Analytic studies, on the other hand, attempt to quantify the relationship between two factors orthe effect of an intervention/exposure on an outcome. In analytic studies, depending onwhether the researcher actively changes a factor or imposes/uses an intervention, determines whether the study is considered to be observational (passive involvement of researcher), or experimental (active involvement of researcher). Experimental studies are analytic studies in which the researcher manipulates the exposure whileallocation of subjects occurs to the intervention or tothe exposure group.

Experimental studies, or randomised controlled trials (RCTs), are similar to experiments in other areas of science. Subjects are allocated to two or more groups to receive an intervention or exposure and then followed up under carefully controlled conditions.

In observational studies, the researcher simply measures the exposure or treatments of the groups. These studies include case–control studies,cohort studies or cross-sectional studies.

These studies all include matched groups of subjects and assess associations between exposures and outcomes.

Studies can incorporate several design elements and thus the control arm of a randomized trial may also be used as a cohort study, while the baseline measures of a cohort study may be used as a cross-sectional study.

How to write a paper?

Two main questions have to be asked prior to witting a paper: what is it important about the paper that we are ready to write and which is the audience that might be interested in our results. Following that, the IMRAD (introduction, material and methods, results, discussion) way of writing needs to be followed, since this is nowadays a standard prerequisite for publication in all major journals.

Each of the above sections of a manuscript needs to be thought as an answer to a specific question: Introduction-why the research question was asked, Materials and methods-what did we do and how, Results-what did we find, Discussion, what does it mean and how does it relate to previouslypublished work.

In the introduction, the first sentence should pick up some or most of the words from the title, it should be clearly explained what was the motivation for the investigation, while the last sentence of the introduction should clearly state the purpose of the study.

By reading materials and methods the reader should be able to replicate what the authors did in their study. In the results section results of the main and secondary outcomes of the study should be reported. In this section there is absolutely no space for interpretation of the findings. This should strictly be performed in the discussion.Illustrations are critical, because figures and tables are the most efficient way to present results, however, no duplication of results between text and tables or figures is allowed.

The discussion section of the manuscript should start with the main finding and be followed by a list of the shortcomings as well as the advantages of the study performed. In turn, a comparison of the findings of the current study with those of previously published studies should be reported. Following that, the authors should explain what do the study results mean for clinical practice as well as they should describe any future research prospects that exist or were created by their study.

What IMRAD does not address are the title, the authors, the abstract, the acknowledgements and the references. A good title should contain the fewest possible words that adequately describe the content of a paper. The abstract of the manuscript is its advertisement and might strongly influence whether or not the work is further considered.It should be as brief as possible, interesting and easy to be understood without reading the whole article.

Currently there are several accepted ways of reporting specific types of trials, such as the CONSORT for randomized clinical trials, the STARD for diagnostic studies, the STROBE for observational studies, the QUOROM, for systematic reviews and the MOOSE for systematic reviews and meta-analysis of observational studies

What should always be remembered is that since most of readers wish to read short, substantial and clear manuscripts every effort should be made by the same people, when they are authors, to write short, substantial and clear manuscripts.

Fresh or frozen embryo transfer

The main factors on which the achievement of pregnancy is dependent on are embryo and endometrium quality. Both of these factors are related to a closely associated third variable: ovarian stimulation.

Currently there is no evidence to support that ovarian stimulation for IVF affects embryo quality. However, there is plenty of evidence suggesting that ovarian stimulation affects endometrial receptivity. High progesterone levels on the day of hCG administration, that are associated with more oocytes and higher E2 levels, affect adversely the probability of pregnancy, as has been recently shown in a meta-analysis of > 60000 IVF cycles. Moreover, high progesterone levels on the day of hCG administration seem to have no effect on embryo quality, as shown by analyzing embryo donation cycles and frozen thawed cycles, in which the embryos transferred originate from cycles with or without high progesterone. More importantly, endometrium studies, at either the histological or the gene expression level, clearly show an adverse effect of ovarian stimulation on endometrial receptivity.

For the above reasons it is tempting to consider the concept of transferring embryos exclusively in the frozen cycle. Data on the comparison between children born after fresh or frozen embryo transfer suggest that many neonatal outcomes, such as small for gestational age, birth weight<2500g, delivery <37 weeks and perinatal mortality are improved after frozen as compared to fresh embryo transfer, while the same is true for maternal obstetric outcomes such as antepartum hemorrhage, which is significantly reduced after a frozen as compared to a fresh transfer.

Regarding the probability of pregnancy after transfer exclusively in the frozen as compared to the fresh cycle, data form a limited number of RCTS suggest that this is higher when transfer occurs exclusively in the frozen thawed cycle as compared to the fresh one. It is not clear, however, whether this higher probability of pregnancy in the frozencycle is a universal effect applicable to all patients and all types of ovarian response. To answer these questions as well as to confirm or deny the current findings further research is required.




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Richard Kennedy *UK*

Regulation in ART

Regulation in healthcare is a relatively new phenomenon and has arisen from a failure of providers to assure its quality and safety in an age of rising public expectations. Industry has provided a model with the airlines leading the way but it took many disasters to make this happen. In health in the UK it took the failings of a paediatric cardiac surgery service in Bristol in 1997 to provide the catalyst. The response to this has occurred during a time of exponentially rising costs, a challenging fiscal environment, instant social communications and a litigenous and demanding culture.

Regulation in the context of healthcare can be defined as the range of factors exterior to the practice or direct administration of medical care that influences the behaviour in delivering or using health services. But why and how do we need to influence behaviour? It has been estimated that up to 10% of all acute healthcare episodes are subject to an adverse event. Many of these have relatively minor consequences. Some have disasterous consequences. All add to healthcare costs due to increased intervention, administration, litigation andsocietal costs through delayed recovery. An example of this in our field is OHSS. Furthermore practitioners may havean inconsistentapproach to management with downstream consequences. An example of this is the number of embryos replaced in an IVF cycle. These behaviours can be modified by a rigorous approach to quality and safety, implementation of practice guidelines and a proactive approach to the management of physician performance.

Regulation can apply toboth individuals and systems. Professional regulation has been in place for clinicians for many years but arguably has failed to deliver the improvements in safety and quality that are essential to improved patient outcomes. We have seen this in examples of multiple fatalities despite personal registration from competent authorities. It is system regulation that has the greatest opportunity for widespread improvements. The UK experience in general healthcare has been chequered and despite the Care Quality Commission regulating hospitals in the UK we have recently witnessed the Mid Staffordshire Disaster. In assisted conception practice the UK has had the Human Fertilisation and Embryology Authority in place since 1991 and a number of other national states have followed suit.

Has regulation in ART improved outcomes for patients? Subjectively the UK sector has advanced scientifically more easily in the regulatory environment and the political and public assurance that this has provided. Furthermore those working in the field have had a clearly defined legal and, to a lesser extent,practice framework within which to operate. However, objectively, benefit is less obvious. Outcomes following ART in the UK are average within the European Community and multiple pregnancy rates are stubbornly high and high profile adverse incidents have occurred. So can a regulatory approach to ART be recommended? In our experience the potential leverage to improve practice has not been realised to the extent that might have been expected despite significant cost. Nevertheless regulation has the potential to deliver significant public health gains and is likely to be more effective than practitioner guidelines and self-regulation.

Joe Leigh Simpson *USA*

Joseph Conaghan *USA*