increased risk for serious infections during the first year of life [18]. The only concern about vaccinations is about live vaccines; it is recommended to postpone these vaccinations after 4-6 months after the last administration of drug during pregnancy.

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SP0149 ASSISTED REPRODUCTION TECHNIQUES: WHAT CAN WE TELL TO WOMEN WITH RHEUMATIC DISEASES?

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Assisted medical procreation includes all the techniques based on the manipulation of reproductive cells that will allow infertile couples to conceive a child. Main techniques are ovulation induction with or without intrauterine insemination, controlled ovarian stimulation and in vitro fertilization (IVF).

Intrauterine insemination: sperm (from partner or donor) is inserted directly into woman's cervix, or uterus at the time of ovulation.

Controlled ovarian stimulation is aimed at stimulate ovarian to allow egg retrieval few hours later. Protocols usually include gonadotropin-releasing hormone agonist or antagonists associated with recombinant follicle-stimulating hormone (with concomitant close ovarian monitoring).

Controlled ovarian stimulation is generally followed by egg retrieval and then by IVF, which is performed in the laboratory by putting into contact collected oocytes with sperm (partner or donor). Intracytoplasmic sperm injection (ICSI) is performed in case of inadequate quality of the partner's sperm (oligospermia notably). One or 2 embryos are transferred in utero 2/3 or 5 days later (or during the next cycle), while other good quality embryos are cryopreserved for later use. There is no difference in the rates of ongoing pregnancy between transfers of frozen or fresh embryos [1].

By definition, an IVF procedure is defined by the transvaginal egg retrieval: even if the X obtained embryos are implanted Y times, this is still counted as the same procedure. A retrospective study of 14,469 women undergoing IVF, found that the cumulative live birth rates by procedure steadily increased with the number of collected oocytes, reaching 70% when ≥ 25 oocytes had been retrieved [2].

Women with auto-immune diseases or inflammatory chronic rheumatism may have infertility as in the general population or because of previous gonadotoxic treatment as cyclophosphamide. While artificial inseminations and oocyte or embryo donations can be considered equivalent to a natural conception in terms of risk, particular attention is needed during IVF in women with systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS) and/or biology (APL) because of the increased level of estradiol after ovarian stimulation (risk of lupus flare and of thrombosis) [3].

Ovulation induction treatments with in vitro fertilization can be safely used in patients with SLE with stable/inactive disease [4]. Similarly, women with rheumatoid arthritis or spondyloarthritis can undergo IVF safely. In case of APS or APL, an adaptation of the treatment is usually required, especially around the egg retrieval. Management of pregnancy (both treatment and monitoring) must be planned before IVF [4].

As for a natural pregnancy, pre-counselling is important to adapt the treatment (interruption of contraindicated drugs in pregnancy as mycophenolate mofetil or

methotrexate before conception due to their potential teratogenicity or at the end of the second trimester for anti TNF agents) [4]. Some treatments, especially hydroxychloroquine in SLE, have to be maintained during all this period and during pregnancy. In women with APS or APL, prophylactic dose of low weight molecular heparin (LWMH) is recommended during the period of stimulation. In case of treatment with coumadine, switch for curative LWMH is needed. In both cases, short interruption is required for the oocyte puncture. Low dose of aspirin is added after the embryo implantation. Folic supplement is recommended, especially in cases of recent treatment with methotrexate of current treatment with sulfasalazine. Immunizations are also important.

Given its potential to reduce the miscarriage rate, LT4 supplementation is recommended for infertile women with subclinical hypothyroidism or thyroid autoimmunity who are undergoing IVF [5].

Finally, a key role of inflammatory immune response has been shown in reproductive failures but a recent meta-analysis did not find any positive effect of immunotherapy (especially anti-TNF) in improving the live birth rate in women undergoing IVF treatment [6].

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SP0150 THE IMPACT OF RHEUMATIC DISEASES AND ANTI-RHEUMATIC DRUGS ON MALE FERTILITY IN ADULT AND YOUNG PEOPLE

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Background: The chronic, systemic inflammation in rheumatic diseases can impair male fertility by direct effects on the gonads or by affecting the hypothalamic-pituitary-gonadal (HPG) axis resulting in hypogonadism. Impaired gonadal function is reflected by reduced sperm quality and sometimes lowered testosterone levels. Drugs may impair fertility by impairing spermatogenesis or interfere with the HPG axis.

Objectives: To summarize the knowledge on the impact of rheumatic disease and its therapy on fertility in adult and pediatric patients

Methods: Search of the literature

Results: No impairment of spermatogenesis has been shown for azathioprine, cyclosporine, and mycophenolate mofetil. Risk of permanent infertility is associated with cytotoxic drugs, particularly the alkylating agent cyclophosphamide. Effects of methotrexate (MTX) on male fertility are related to dose. There is no indication that low-dose MTX 5 – 25 mg/week impairs male fertility. Case reports of men with psoriasis treated with low-dose MTX have either found completely normal sperm quality or detected oligo- and azoospermia.

Cyclophosphamide (CYC) is administered to adult and pediatric patients with systemic lupus erythematosus, other connective tissue disease and vasculitides. Gonadal damage by CYC is dose-dependent revealed by oligo- and azoospermia

as well as low testosterone, low inhibin B and elevated FSH levels. Cumulative doses of $> 7.5\text{g/m}^2$ carry a high risk of permanent infertility in adults. In survivors of childhood cancer treated with CYC recovery of spermatogenesis was sometimes seen after many years.

Sulfasalazine (SZ) can induce transient infertility with oligospermia, abnormal morphology of sperm cells and reduced sperm motility in about 40-86% of treated men. Plasma levels of steroids and gonadotropins remain normal during SZ therapy. Recovery of normal sperm quality is observed one to three months after discontinuation of SZ.

Studies comparing men treated with TNF inhibitors (TNFi) with disease-matched and/or healthy controls did not find impairment of sperm quality neither after short term or long-term treatment. Several studies found significantly better sperm quality in patients receiving long-term TNFi therapy than untreated disease matched controls.

Conclusion: Rheumatic disease has an impact on male fertility both by the disease process and by therapy. Most antirheumatic drugs have no negative effect on reproduction, however, treatment with cyclophosphamide increases the risk of infertility both in adults and pediatric patients. Increasing awareness about reproduction issues and infertility risk is needed among adult and pediatric rheumatologists. Clinicians should actively involve themselves in counseling their patients.

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FRIDAY, 14 JUNE 2019

15:30:00 – 17:00:00

The future of therapeutic strategies

SP0151 MICROFABRICATION TECHNOLOGIES FOR CARTILAGE REPAIR

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Background: Cartilage trauma is a major risk factor for the development of post-traumatic osteoarthritis. Treatment options are limited, are ineffective in the long run or come with disadvantages. Hence unconventional new strategies need to be explored to address this problem.

Objectives: In this lecture, I will present three strategies that are currently explored in my lab and that rely on the integration of biology with micro- and nanotechnologies to solve this problem.

Results and Methods: In a first strategy, we invested in the development of injectable and in situ gelating hydrogels that can be used as fillers of a cartilage defect stimulating its regeneration. We developed a panel of natural polymer (e.g. hyaluronic acid, dextran, heparin, gelatin, collagens) – tyramine conjugates which crosslink in a macromolecular network in an enzymatic reaction. The reaction is fast, can be tuned and using this method a wide variety of extracellular matrix mimics can be engineered. Moreover, the crosslinking reaction fixates the gel in the surrounding tissue through covalent bonding between tyramine residues in the hydrogel with tyrosine residues in extracellular matrix proteins, effectively acting as a glue. The hydrogel can be applied during an arthroscopic procedure. We tested the potential of the hydrogel to facilitate the repair of an acute focal cartilage defect in an equine chondral defect model and evaluated the repair process after 2 weeks, 3 months and 7 months. We compared the repair of a hydrogel-filled defect with the microfracture procedure, a frequently used but largely ineffective procedure due to the formation of fibrous cartilage instead of hyaline cartilage. After two weeks massive cell ingrowth in the hydrogel was observed. This continued and after 3 months hydrogel treated defects resulted in near complete defect filling with predominantly hyaline cartilage and without noticeable reactions in the subchondral bone. This was in marked contrast to the defects treated with microfracture, which showed a massive response in subchondral bone and the formation of fibrous tissue. The repair was consolidated after 7 months. Defect filling might be a viable solution for treatment of focal cartilage defects to prevent early onset, post-traumatic osteoarthritis.

In a second strategy, we use the same material platform for cell delivery in the joint. Co-injection of cells with the in situ gelating hydrogels might be beneficial in the repair of particularly large (osteo)chondral defects. We have developed

microfluidic-based systems for the encapsulation of 10-15 cells in microgels of approximately $100\mu\text{m}$ or even at the single cell level in microgels with a diameter of $30\mu\text{m}$ slightly larger than the cell itself. We postulated that encapsulation of Mesenchymal Stromal Cells (MSCs) could prolong the retention time in the joint after an intra-articular injection over "naked" MSCs and may, therefore, improve the therapeutic benefit of these cells. We tested this hypothesis in a rat model and indeed showed that, while "naked" near infrared labeled MSC rapidly disappeared from the injected joint, encapsulated cells remained present up to 4 months. We are currently exploring its potential to improve the therapeutic efficacy of the MSCs.

In a third strategy, we use the material platform in combination with cytokine neutralizing antibodies to generate easily injectable microgels that can sequester pro-inflammatory cytokines from the synovial fluid. Rather than using conventional antibodies, we rely on the variable domain of single chain, heavy chain-only antibody fragments such as found in Camelidae. These antibody fragments can be easily produced using recombinant DNA technology and are open for a wide variety of chemical reactions without impacting its biological activity. These microgels can effectively neutralize cytokines in cell assays in vitro and are currently explored for its potential to neutralize cytokines in synovial fluid and after intra-articular injection.

Conclusion: In conclusion, the integration of biology with microfabrication technologies has the potential to generate the next generation of therapies for the treatment of cartilage defects and osteoarthritis.

Disclosure of Interests: None declared

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SP0152 3D PRINTED DRUGS

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Background: With the advent of personalised medicine, the need for flexible dosing is increasingly important. Conventional pharmaceutical manufacturing processes can be constrained in their ability to offer flexible dosing options to meet patient need. This is particularly important in specific populations, for example children, where available formulations are frequently not age-appropriate and need to be modified to achieve an intended dose. 3D-printing of solid dosage forms offers a disruptive technology which enables solid-dosage forms of medicines to be manufactured at flexible, precise doses meeting the needs of individual patients. This technology has relevance for manufacture of existing active pharmaceutical ingredients for a range of conditions including inflammatory diseases.

Objectives: To develop 3D-printed oral solid dosage forms of medicines which are age-appropriate for children and young people. To determine the acceptability of 3D-printed medicines to children and young people by conducting interventional studies of tablet administration.

Methods: Tablets containing a range of active pharmaceutical ingredients (API) were produced using two stages: (i) hot melt extrusion of a filament containing API and excipients; (ii) 3D printing of the filament using fused deposition modelling (FDM) to produce the desired shape in a layer-by-layer pattern. Acceptability of 3D-printed tablets to children and young people (CYP) aged 4-12 years was assessed by the swallowability and mouthfeel following administration of different size 3D-printed placebo tablets.

Results: Using hydrocortisone as an exemplar API, Tablets were successfully produced by the FDM 3D printing process. Thermal analysis indicated that HC remained stable below 160°C and the tablets had very high mechanical strength with friability of 0%. This illustrates the ability of the printer to produce a ready-to-use-tablet without the need for a drying or finishing step. The disintegration took 9.2–14 min confirming immediate release properties. We administered for the first time globally an ingestible 3D-printed tablet to a child. CYP were able to swallow and ingest 3D-printed bi-convex tablets of either 6mm, 8mm or 10mm diameter. The 3D tablets were reported by CYP to have a slightly more discernible mouthfeel than placebo tablets of the same size manufactured in a GMP facility.

Conclusion: FDM 3D printing offers a disruptive technology for the manufacture of solid dosage forms of medicines of flexible doses with excellent dose precision and pharmacopeial properties. In circumstances where modification of existing dosage forms is needed, this offers an alternative reliable means of achieving the intended dose. This technology is also suited to the manufacture of solid dosage forms of small molecules which may be particularly important in the treatment of inflammatory disease.

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