Nutritional pattern and female fertility

Paolo Emanuele Levi Setti [1,2]

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HUMANITAS
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Since the 90's **Preconceptional health care** has become a topic of considerable interest.

ELSEVIER

Preconceptional health care model

Alexander D. Allaire, Robert C. Cefalo*

Division of Maternal–Fetal Medicine, Department of Obstetrics and Gynecology, University of North Carolina, CB No. 7570, MacNider Building, Chapel Hill NC 27599-7570, USA

European Journal of Obstetrics & Gynecology and Reproductive Biology 78 (1998) 163–168

OBSTETRICS & GYNECOLOGY

The idea of preconceptional health care encompasses all women capable of becoming pregnant.

The program identifies maternal/paternal conditions that may potentially be detrimental to the mother or fetus and recommends necessary medical, behavioral or education changes which may increase the likelihood of optimal maternal and fetal outcomes.

from the association ADA REPORTS

Position of the American Dietetic Association: Nutrition and Lifestyle for a Healthy Pregnancy Outcome

J Am Diet Assoc. 2008;108:553-561.

Environment Dictating A Need For Position:

With more than one third of all women being obese, achieving good pregnancy outcomes can be difficult

To optimize the health outcomes of both mother and child, women of childbearing age **should begin pregnancy in good nutritional status**.

KEY POINTS:

A. Optimizing Outcomes through Good Nutrition and Health before Pregnancy

B. Weight Gain during Pregnancy

C. Food and Physical Activity Guidance during Pregnancy

D. Appropriate and Timely Vitamin and Mineral Supplementation

Comprehensive Invited Review

Redox Considerations in Female Reproductive Function and Assisted Reproduction: From Molecular Mechanisms to Health Implications

ASHOK AGARWAL, SAJAL GUPTA, LUCKY SEKHON, and RANI SHAH

ANTIOXIDANTS & REDOX SIGNALING
Volume 10, Number 8, 2008

The role of oxidative stress in female reproduction is becoming increasingly important

Free radicals and OS have an important role in modulating many physiological functions in reproduction:

- Infertility
- Endometriosis
- Abortion
- Hydatidiform mole
- Embryopathies
- Pregnancy complications such IUGR and preeclampsia.

human reproduction update

Role of micronutrients in the periconceptional period

I. Cetin[1,2,3], C. Berti[1,2], and S. Calabrese[1,2]

Human Reproduction Update, Vol.16, No.1 pp. 80–95, 2010

BACKGROUND: Micronutrient deficiencies have been associated with significantly high reproductive risks, ranging from infertility to fetal structural defects and long-term diseases. In this review we focus on the reproductive risks related to some micronutrients during the periconceptional period, a critical step in determining fetal development and health due to the potential onset of several disorders.

RESULTS: Fertility, conception, implantation, fetal organogenesis and placentation are the critical stages potentially affected by nutrition during the periconceptional period. Reactive oxygen species (ROS) and total homocysteine (tHcy) plasma levels are factors involved in the respective mechanisms. The preconceptional period is particularly important since it affects both fertility and the early stages of gestation. Micronutrients' dietary intake and maternal status affect the different phases of the onset and development of pregnancy as well as of the conceptus.

CONCLUSION: Although human studies are scarce, and conclusive evidence is provided solely for periconceptional folate and prevention of neural tube defects (NTDs), the overall data indicate that micronutrients may affects fertility, embryogenesis and placentation, and the prophylactic use of some micronutrients may be useful in preventing several adverse pregnancy outcomes. Efforts to increase awareness of a healthy diet should be strengthened not only throughout pregnancy but also before. However, further researches in humans are necessary to optimise periconceptional micronutrient requirements.

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THE COCHRANE COLLABORATION®

Preconception lifestyle advice for people with subfertility (Review)

Anderson K, Norman RJ, Middleton P

There is **no current guideline** about what preconception advice should be offered to people presenting for infertility treatment.

Factors that may affect fertility and the chance of a healthy, live birth include: weight, diet, vitamin intake, iodine intake, alcohol intake, caffeine intake, smoking, other substance abuse, environmental pollutants, infections, medical conditions, medications and family medical history

Given the lack of RCTs evaluating the effectiveness of preconception lifestyle advice, this review cannot provide guidance for clinical practice in this area.

This review found no evidence from controlled clinical trials about the effect of preconception advice on the chance of a live birth in subfertile people.

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Obesity and reproduction: a committee opinion

Practice Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

Fertility and Sterility® Vol. 104, No. 5, November 2015

TABLE 1

Categories of obesity by body mass index.[a]

Category	BMI (kg/m^2)
Underweight	Less than 18.5
Normal	18.5 to 24.9
Overweight	25.0 to 29.9
Obesity, Grade I	30.0 to 34.9
Obesity, Grade II	35.0 to 39.9
Obesity, Grade III	≥40.0

Note: BMI = body mass index.
[a] WHO 2004.

Practice Committee. Obesity and reproduction. Fertil Steril 2015.

- MENSTRUAL CYCLE ABNORMALITIES
- OVULATORY DYSFUNCTION
- ALTERED OVARIAN RESPONSIVENESS AND OOCYTE QUALITY
- ALTERED ENDOMETRIAL FUNCTION
- MISCARRIAGE
- MATERNAL-FETAL ENVIRONMENT

- Preconceptional counseling for obese couples should address the reproductive and maternal-fetal consequences of obesity

- The health benefits of postponing pregnancy to achieve weight loss must be balanced against the risk of declining fertility with advancing age of the couple

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ELSEVIER
Reproductive BioMedicine Online (2015) 31, 30–38

The impact of food intake and social habits on embryo quality and the likelihood of blastocyst formation

- *The quality of the embryo and the likelihood of blastocyst formation were negatively influenced by the consumption of alcoholic drinks and by smoking habits*
- *The consumption of red meat had a negative effect of embryo development*
- *Intake of cereals, vegetables and fruits led to better embryo development*
- *Extremely low or high BMI were shown to be inversely correlated with treatment success*

human reproduction ORIGINAL ARTICLE *Reproductive biology*

Amino acid composition of human uterine fluid: association with age, lifestyle and gynaecological pathology

Alexandra J. Kermack[1,2,3,4], Sarah Finn-Sell[1,2], Ying C. Cheong[2,3], Nicholas Brook[3], Judith J. Eckert[1,2], Nick S. Macklon[2,3,4], and Franchesca D. Houghton[1,2,*]

Human Reproduction, Vol.30, No.4 pp. 917–924, 2015

WHAT IS KNOWN ALREADY: Murine, bovine and ovine uterine amino acid content has been reported, but no reliable data on the human exist. Murine studies have demonstrated that the intrauterine periconceptional nutritional environment is affected by maternal diet.

STUDY DESIGN, SIZE, DURATION: Uterine secretions were aspirated from 56 women aged 18–45 years. The women were recruited preoperatively from gynaecological theatre operating schedules or hysterosalpingo-contrast-sonography (HyCoSy) lists. A proportion of these women had proven fertility; however, the majority were being investigated for subfertility. The BMI, gynaecological history and dietary pattern of these women were also assessed.

MAIN RESULTS AND THE ROLE OF CHANCE: The profile of 18 amino acids in uterine fluid was described. In total, human uterine fluid was observed to contain an amino acid concentration of 3.54 mM (interquartile range: 2.27–6.24 mM). The relative concentrations of 18 amino acids were not significantly altered by age, BMI, cycle phase or the presence of specific benign gynaecological pathologies. However, a diet identified by a validated scoring system as being less healthy was associated with higher concentrations of asparagine ($P = 0.018$), histidine ($P = 0.011$), serine ($P = 0.033$), glutamine ($P = 0.049$), valine ($P = 0.025$), phenylalanine ($P = 0.019$), isoleucine ($P = 0.025$) and leucine ($P = 0.043$) in the uterine fluid compared with a healthier diet, defined as one with a higher intake of fresh vegetables, fruit, whole-grain products and fish and a low intake of red and processed meat and high fat dairy products. There were no significant correlations between serum amino acid concentrations and those in the uterine fluid.

WIDER IMPLICATIONS OF THE FINDINGS: These findings increase our understanding of the nutritional environment encountered by the preimplantation embryo, and indicate how periconceptional diet may alter this. Given the importance of early embryo environment for programming of development and future health, this information may aid in the development of nutritional interventions aimed at optimizing the preimplantation phase of human embryo development *in vivo*.

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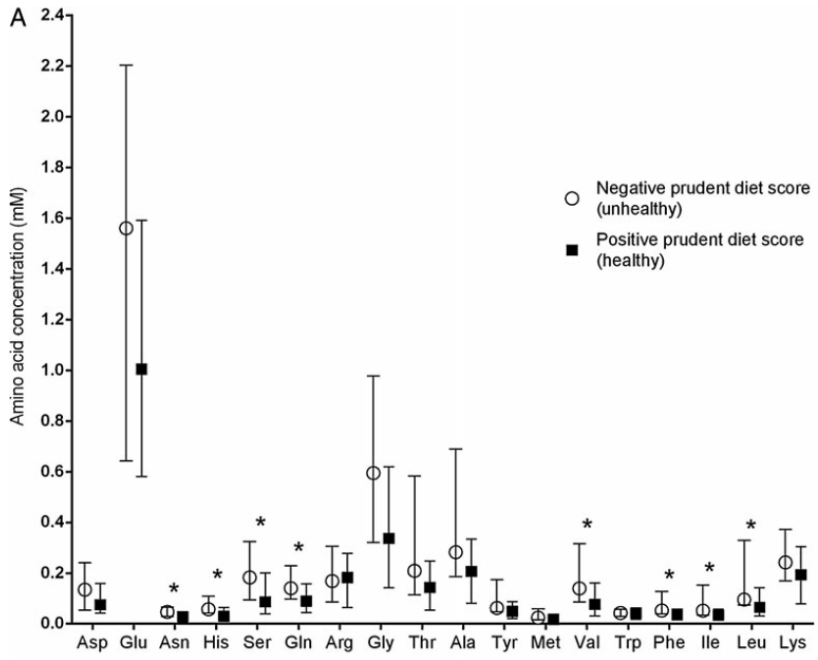
Human Reproduction, Vol.30, No.4 pp. 917–924, 2015



A significant difference in the uterine fluid concentration of eight amino acids between women with a positive prudent diet score (healthy diet) when compared with those with a negative one (unhealthy diet); asparagine ($P < 0.018$); histidine ($P < 0.011$); serine ($P < 0.033$); glutamine ($P < 0.049$); valine ($P < 0.025$); phenylalanine ($P < 0.019$); isoleucine ($P < 0.025$); and leucine ($P < 0.043$).

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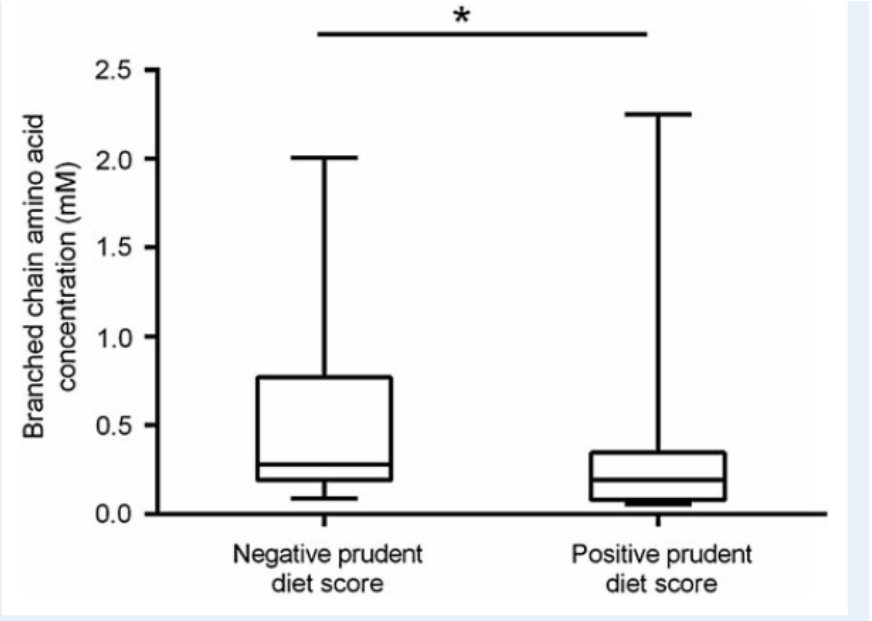


The amino acid content of human uterineW fluids is stable through the menstrual cycle, and changes little with increasing reproductive age, BMI or in the presence of a number of benign pathologies.

In contrast diet is shown to alter amino acid concentration in the uterine fluid and hence, presumably, the nutritional composition within the reproductive tract during preimplantation embryo development

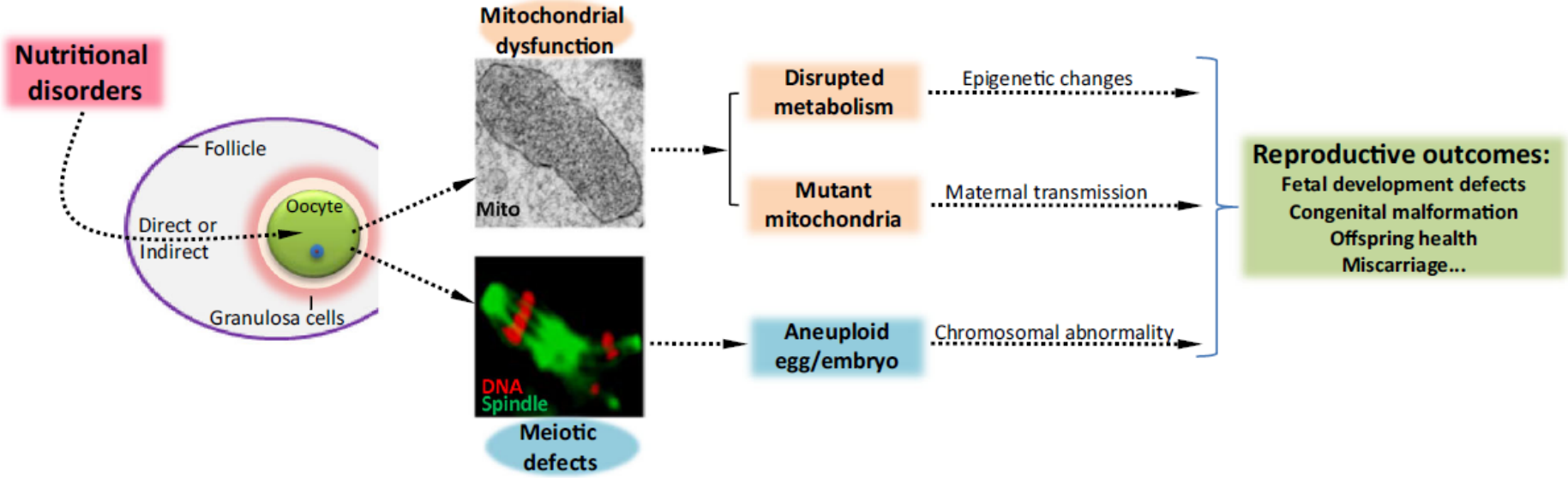
Cellular and Molecular Life Sciences

REVIEW

Metabolic control of oocyte development: linking maternal nutrition and reproductive outcomes

Cell. Mol. Life Sci. (2015) 72:251–271

Ling Gu · Honglin Liu · Xi Gu · Christina Boots · Kelle H. Moley · Qiang Wang



Metabolic disorders, such as obesity and diabetes, have major adverse effects on fertility, pregnancy, and the health of offspring

Introduction:
Microbiome in human reproduction

Jason M. Franasiak, M.D.[a,b] and Richard T. Scott, Jr., M.D., H.C.L.D.[a,b]
Fertility and Sterility® Vol. 104, No. 6, December 2015

The second human genome
The human body contains 10-fold more microbial cells than the human cells and accounts for 1%–3% of our total body mass.

Data has been gathered on the microbiome at every stage and level of human reproduction from the ovary, follicle, and oocyte; to testes and semen/spermatozoa; and to the fallopian tube, uterus, cervix, and vagina.

Both the male and female reproductive tracts exhibit complexity and diversity only realized within the last decade.

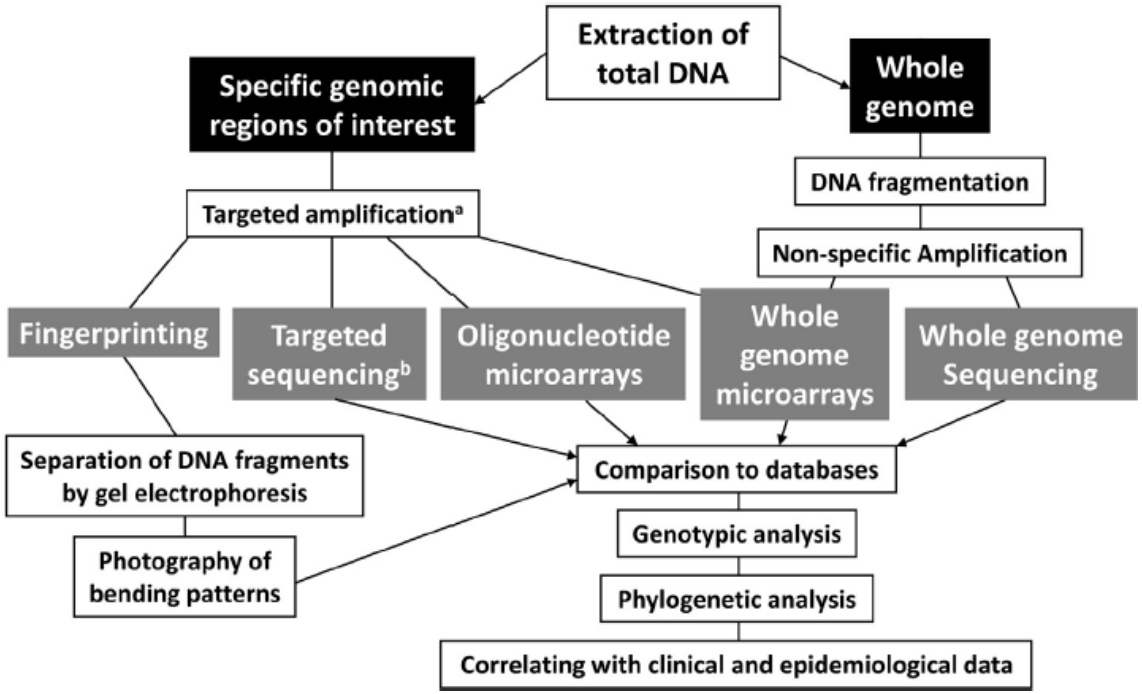
Bacteria are not simply free-floating on the surface of tissue, but form their own three-dimensional biofilms with inner and outer layers, adds an additional complexity and could be of great importance if they were further explored

Molecular characterization of the human microbiome from a reproductive perspective

Amir Mor, M.D., Ph.D.,[a] Paul H. Driggers, Ph.D.,[b] and James H. Segars, M.D.[b]

Fertility and Sterility® Vol. 104, No. 6, December 2015

Common molecular biology techniques used to characterize microbiome diversity and function.



An unbalanced microbiome has been associated with multiple pathologic conditions, such as infertility, susceptibility to infections, cancers, autoimmune diseases, and even neuro-psychiatric disorders.

In the field of reproduction, the characterization of vaginal, cervical, and intrauterine "**healthy core microbiome"** vs. an unbalanced one has the potential to improve ART.

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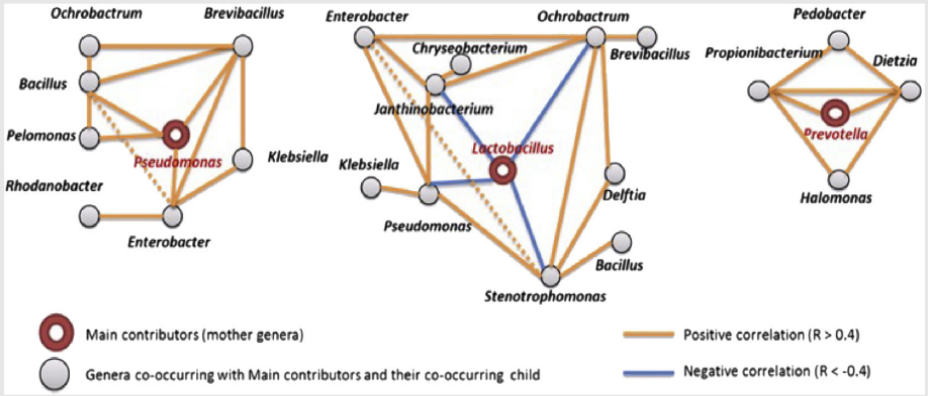
Reproductive tract microbiome in assisted reproductive technologies

Jason M. Franasiak, M.D.,[a,b] and Richard T. Scott, Jr., M.D., H.C.L.D.[a,b]
Fertility and Sterility® Vol. 104, No. 6, December 2015

INTERACTIONS BETWEEN THE MICROBIOME AND THE REPRODUCTIVE AXIS

The study of the microbiome and its relationship to the efficiency of conception and early pregnancy maintenance is just beginning

- Vaginal Microbiome
- Uterine Microbiome
- Ovarian Follicle Microbiome



The overall microbiome interacts with the dominant species. The dominant species causes clusetering of other species around it. This dynamic may have an impact on outcomes data (33).

This environment may affect gametogenesis and that it changes with hormonal milieu leading into the time of embryo transfer and implantation suggests that it very likely plays an important role that we are just beginning to comprehend and understand.

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Maternal microbiome and pregnancy outcomes

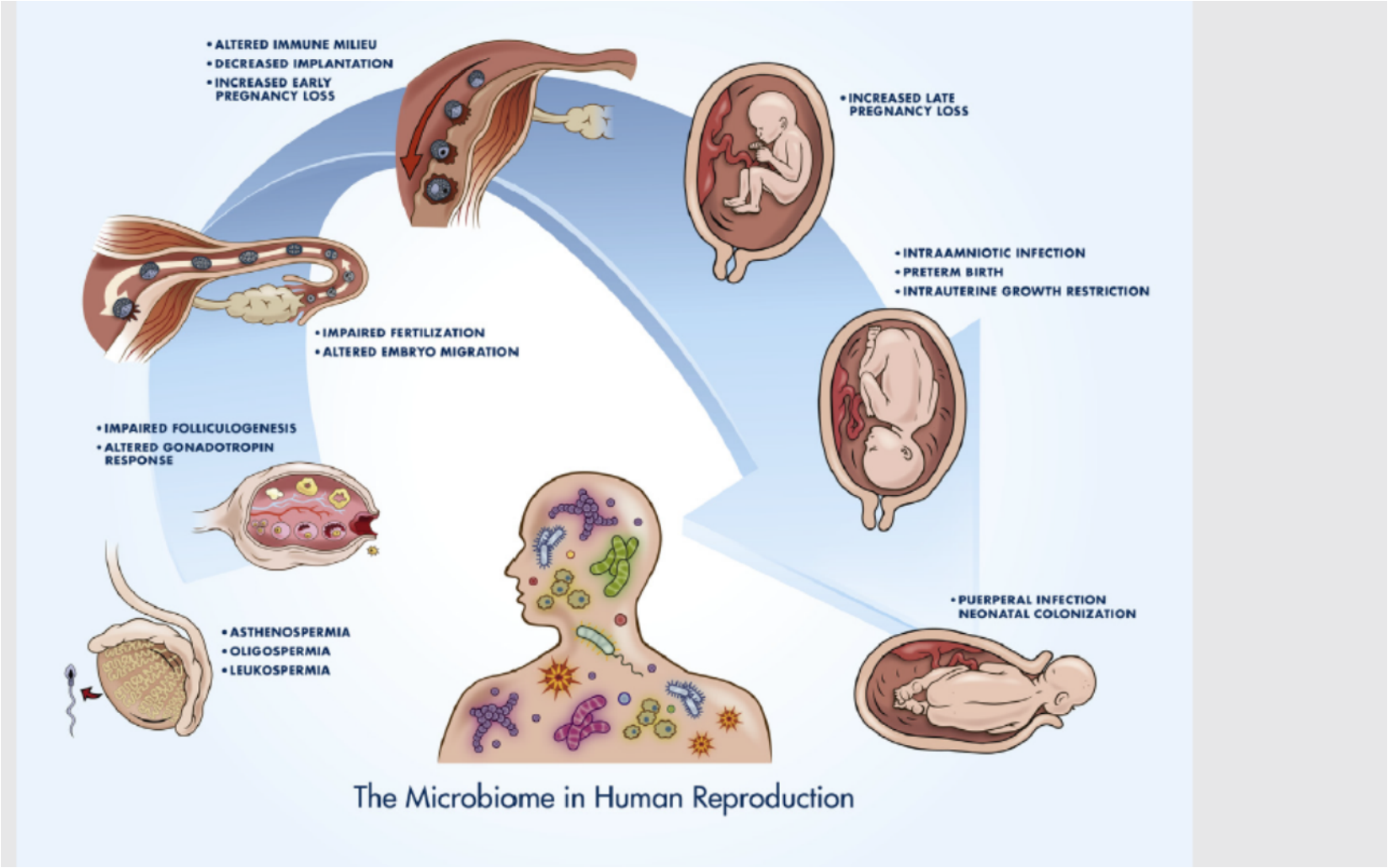
Chelsea Fox, M.D.[b] and Kacey Eichelberger, M.D.[a]
Fertility and Sterility® Vol. 104, No. 6, December 2015

- NONGRAVID VAGINAL MICROBIOME
- GRAVID VAGINAL MICROBIOME
- PLACENTAL MICROBIOME
- THE HUMAN MICROBIOME AND PRETERM BIRTH
- HUMAN HOST SUSCEPTIBILITY

Although we have recognized the existence of bacteria for > 330 years, it is truly only within the past 7 years that we have begun to genetically characterize the bulk of that biome.

Metagenomic studies have begun to characterize the healthy vaginal and gut microbiomes in the nongravid and gravid state, as well as the rich diverse placental microbiome

At its current stage, there are no immediate clinical applications of microbiota-based research and clinical obstetrics.



Franasiak. Microbiome in reproduction. Fertil Steril 2015.

Lifestyle factors that affect infertility.

Factor	Impact on fertility	Study
Obesity (BMI >35)	Time to conception increased two-fold	Hassan and Killick, 2004 (53)
Underweight (BMI <19)	Time to conception increased four-fold	Hassan and Killick, 2004 (53)
Smoking	RR of infertility increased 60%	Clark et al., 1998 (38)
Alcohol (>2 drinks/day)	RR of infertility increased 60%	Eggert et al., 2004 (50)
Caffeine (>250 mg/day)	Fecundability decreased 45%	Wilcox et al., 1998 (58)
Illicit drugs	RR of infertility increased 70%	Mueller et al., 1990 (64)
Toxins, solvents	RR of infertility increased 40%	Hruska et al., 2000 (67)

Note: Table reprinted from the document of the same name, last published in 2008, Fertil Steril 2008;90(Suppl):S1-6. BMI = body mass index; RR = relative risk.

Practice Committee. Optimizing natural fertility. Fertil Steril 2013.

American Society for Reproductive Medicine, Practice Committee. Optimizing natural fertility. Fertil Steril 2013.

Lipid Concentrations and Couple Fecundity: The LIFE Study

(J Clin Endocrinol Metab 99: 2786–2794, 2014)

	Overall (n = 501)[a] Median (IQR)	Observed Pregnancy in 12 Months of Follow-Up (n = 347) Median (IQR)	Not Pregnant (n = 154)[b] Median (IQR)	*P* Value
Female				
Cholesterol, mg/dL	180 (42)	177 (43)	182 (40)	.25
Free cholesterol, mg/dL	45 (12)	44 (11)	46 (14)	.04
Phospholipids, mg/dL	222 (44)	221 (44)	223 (45)	.59
Triglycerides, mg/dL	101 (73)	100 (68)	101 (87)	.90
Total lipids, mg/dL	606 (145)	601 (139)	612 (158)	.21
Male				
Cholesterol, mg/dL	190 (49)	185 (46)	198 (50)	.002
Free cholesterol, mg/dL	49 (15)	48 (15)	52 (15)	.009
Phospholipids, mg/dL	222 (51)	219 (50)	226 (53)	.07
Triglycerides, mg/dL	175 (143)	168 (146)	189 (151)	.19
Total lipids, mg/dL	692 (222)	679 (220)	708 (244)	.19

Abbreviation: IQR, interquartile range.

Serum free cholesterol levels were higher on average among male and female partners of couples who did not became pregnant during the study follow-up suggest that serum free cholesterol concentrations in both men and women have an effect on time to pregnancy (TTP).

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While it is widely accepted that many adult disorders have their origins in early development (Gluckman and Hanson, 2004), it is increasingly apparent that maternal nutrition in the periconceptual period can affect oocyte quality (Machtinger et al., 2012), embryo development and offspring health (Connor et al., 2012).

The ovarian follicle provides nutrients for the developing oocyte. Glucose present in the follicular cavity is converted to pyruvate by cumulus cells that surround the oocyte, which is then transported into the oocyte where it is oxidized to provide ATP (Leese and Barton, 1984).

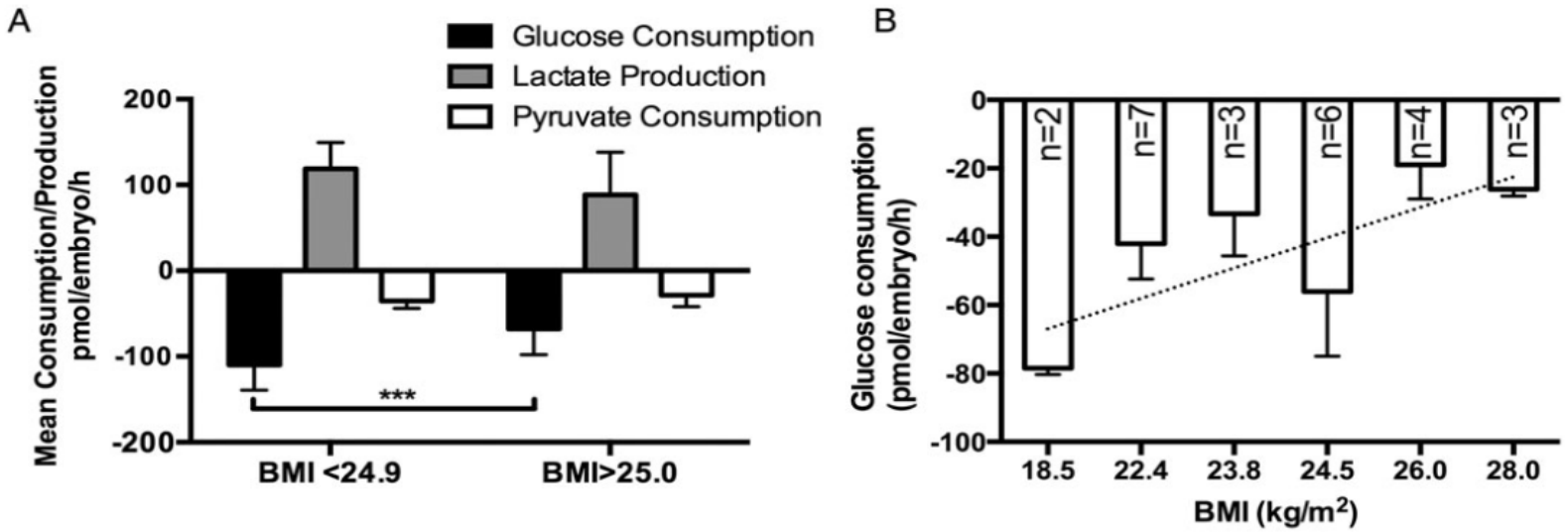
In addition, mammalian oocytes contain a significant endogenous triglyceride repository (Sturmey et al., 2009) that provides a source of metabolic energy during oocyte maturation (Sturmey and Leese, 2003; Ferguson and Leese, 2006; Dunning et al., 2010).

Human Reproduction, Vol.30, No.1 pp. 122–132, 2015
Advanced Access publication on November 12, 2014 doi:10.1093/humrep/deu276

human reproduction ORIGINAL ARTICLE *Reproductive biology*

Human embryos from overweight and obese women display phenotypic and metabolic abnormalities

Christine Leary[1,2], Henry J. Leese[1], and Roger G. Sturmey[1,*]



Embryos from women with a BMI in excess of 25 kg/m2 consumed significantly less glucose than embryos from women of a healthy weight at equivalent stages of development (P , 0.001), whilst there were no significant changes in pyruvate uptake and lactate formation

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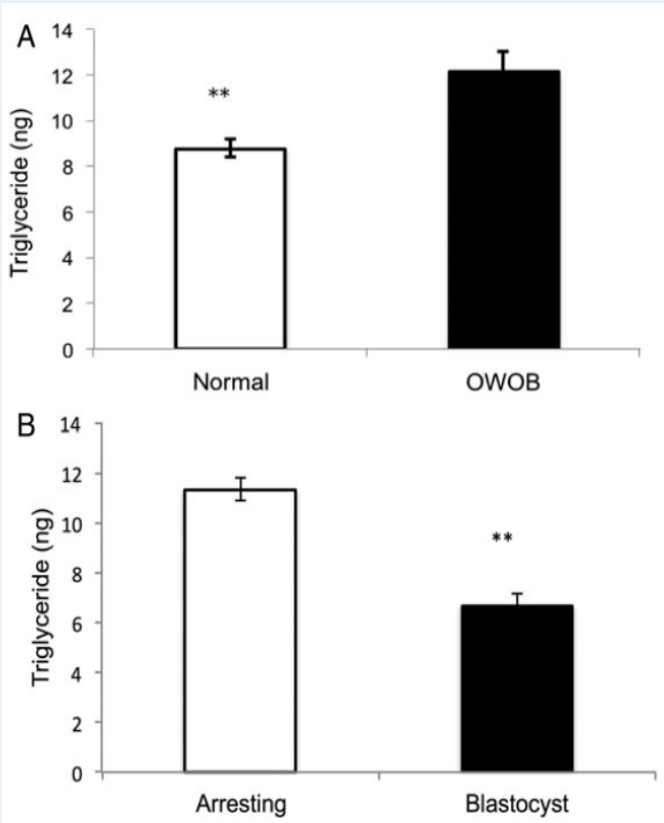
Triglyceride content of human embryos is influenced by maternal BMI.

(A) Embryos derived from oocytes collected from OW/OB women contain significantly *more triglycerides* than those from healthy weight women .

(B) Embryos that arrested prior to the blastocyst stage contain significantly more triglyceride than those capable of forming blastocysts (P = 0.001).



HUMANITAS RESEARCH HOSPITAL

Conclusions

Knowledge regarding the interactions between nutritional patterns, the microbiome and the human reproductive axis is growing rapidly.

A deeper understanding of normal physiology, identification of different dysbioses and metabolic pathways, and characterizing the microbiome's and nutritional impact on reproductive outcomes promises meaningful enhancements in clinical care.

A prudent diet described as diet characterized by higher intakes of fresh vegetables, fruit, whole-grain products and fish and lower intakes of red and processed meat and high fat dairy products is accepted as a reproductive safe diet.

Take home messages

An equilibrium among different mechanisms and their interaction are probably the key of understanding reproductive adaptation, evolution and reproductive wellness, where a deficit is wrong but an excess may be worst.

While much has been learned since the early contributions of folic acid in neural tube defects, the most insightful and powerful findings may lie just ahead. Morphocinetic time lapse embryo evaluation is now available and his role open to be explored.

We just know that we just don't know anything,
then at least don't harm woman life.