Risk of stillbirth is four times higher after in-vitro fertilization (IVF) with or without intra-cytoplasmic sperm injection (ICSI) compared to spontaneous pregnancies.

Dr Wisborg, who is a consultant in the neonatal and intensive care unit at Aarhus University Hospital (Aarhus, Denmark), and colleagues analyzed data that had been collected prospectively from unselected, pregnant women taking part in the Aarhus Birth Cohort. The study included information on women booked for delivery between August 1989 and October 2006. Information on obstetric history, including waiting times to pregnancy and fertility treatments, age, smoking habits during pregnancy, alcohol and coffee intake during pregnancy, marital status, education and any psychological problems was collected in two questionnaires completed before the first routine antenatal visit at 16 weeks gestation. Of note here the complete absence of any data relating to placenta either during the pregnancy or after the birth of the baby. It is so inexcusable and yet so much the “standard of care” that defies logic. For any researcher who tries to explain fetal death and neonatal suffering neglecting completely to examine any placental data is indeed appalling. There is an excuse of course for Dr. Wisborg. He is a neonatologist and it is very probable that he has seen very few placentas in his scientific life if any! I sound sarcastic here and you are right if you thought so. I am sarcastic because I cannot accept the ongoing neglect of the placenta as an important source of information – if not the only one – by the scientific community at large.

The study of over 20,000 singleton pregnancies, published in Europe's leading reproductive medicine journal *Human Reproduction*, found a four-fold (400%) increased risk of stillbirths for women who had IVF/ICSI compared with women who conceived spontaneously or after fertility treatment that did not involve IVF or ICSI. This means that 2-4% of IVF/ICSI pregnancies end up in stillbirth. This is serious matter. However, what makes this finding more important is that the babies who die represent only a small fraction of the total number of babies that are affected in such pregnancies. For every baby that dies in utero, there are at least 5 babies if not more that get very close to death but they survive. These babies almost invariably suffer long-term physical and developmental delays with chronic health problems for the rest of their lives. However, the authors of the Danish study say that these results should be interpreted carefully. Dr Kirsten Wisborg, who led the study, said: "It is important to remember that the risk of stillbirth is still very low among women pregnant after IVF/ICSI. At this stage we do not know whether the increased risk in women pregnant after IVF/ICSI is due to the fertility treatment or to unknown factors pertaining to couples who undergo IVF/ICSI. This needs further investigation." What a relief! At least, Dr. Wisborg gave IVF treatment the benefit of doubt. This was a wise statement as I expect him to realize some time in the future that the cause is not the IVF process but the reason for which a patient undergoes IVF. Patients who undergo IVF due to male factors, tubal occlusion factors and for reasons of sexual preference (lesbian couples) the outcomes do not differ between IVF and spontaneously conceived pregnancies. Our long

experience of more than 20 years has taught us that patients with otherwise unexplained infertility and patients with implantation failure and early pregnancy loss are the ones who end up with complicated pregnancies and stillbirth.

Out of a total of 20,166 singleton, first-time pregnancies, 16,525 (82%) were conceived spontaneously after less than 12 months, 2,020 (10%) after more than a year of trying (classified as sub-fertile), 879 (4%) conceived after non-IVF fertility treatment and 742 (4%) conceived after IVF/ICSI. There were a total of 86 stillbirths, giving an overall risk of stillbirth of 4.3 per thousand pregnancies. The risk of stillbirth in women who conceived after IVF/ICSI was 16.2 per thousand; in women who conceived after non-IVF fertility treatment it was 2.3 per thousand; in fertile and sub-fertile women, the risk was 3.7 per thousand and 5.4 per thousand respectively. One has to take these statistics with not a grain but a lot of salt! It is well established in the serious scientific community that adverse perinatal events including fetal and maternal deaths are severely underreported for many reasons. This paper is not the forum to discuss why such underreporting happens. Such adverse events are estimated to be underreported in the central databases by a factor of 3. In other words, the stillbirth and other adverse outcomes might be as much as 3 times more than reported by the national birth statistics (CDC, NIH etc.)

Dr. Wisborg said: "After adjusting for maternal age, body mass index, education, smoking habits and alcohol and coffee intake during pregnancy we found a significant, four-fold increased risk of stillbirth in women who conceived after IVF/ICSI compared with fertile women. The risk of stillbirth in sub-fertile women and women who conceived after non-IVF fertility treatment was not statistically significantly different from the risk in fertile women. This is most likely the result of insufficient numbers. In our experience, sub-fertile women are at increased risk in relation to normal fertility women and decreased risk in relation to IVF pregnancies. It is all a matter of the degree of the underlying cause of the infertility problem. Patients who end up with IVF treatment are the ones with most underlying issues, which prevent them from conceiving. These same issues are the ones that cause the stillbirth and the other neonatal adverse outcomes that the authors did not evaluate in this study. Such issues are almost exclusively the result of genetic and acquired thrombophilic imbalances that cause placental thrombosis, degeneration and placental insufficiency.

Dr. Wisborg goes on to state: "Until now, there has been speculation that the increased risk of adverse outcomes, such as stillbirths, in assisted reproduction might be due to factors related to the underlying infertility of the couples. However, we found the risk was similar between sub-fertile couples, women who had conceived after non-IVF fertility treatment and fertile couples. This may indicate that the increased risk of stillbirth is not explained by infertility and

may be due to other, as yet unexplained factors, such as the technology involved in IVF/ICSI or some physiological difference in the couples that require IVF/ICSI." It is unfortunate but Dr. Wisborg is a victim of what is known in statistics as a type II error. When we cannot find a difference between two causes of an event, due to insufficient number of study subjects, this is called a type II error. She should never take as a fact that there is no difference between sub-fertile and fertile couples in the rate of stillbirth just because she failed to find such a difference with her study. When one tries to compare events with frequency of 2-4 per thousand (according to her data in this study) one would need thousands of patients in each group in order to reliably state that no difference was found between the sub-fertile and fertile groups. Instead Dr. Wisborg studied only a few hundred of patients in each group. This is scientifically unacceptable. If I had reviewed this paper as a reviewer prior to publication, I would never approve it unless this statement was changed as follows: “we did not find any differences in stillbirth between sub-fertile and fertile groups; this is most likely a type II error due to inadequate numbers for such a comparison”. What surprises me is that, as you will see below, Dr. Wisborg is aware of the numbers problem. She simply failed or intentionally chose to not interpret the results appropriately. This is called “investigator’s bias”. This is one of the major problems with scientific research when the research is done in order to have a result that supports the researcher’s preconceived beliefs and not for the shake of scientific advancement. By doing so, she failed to see that indeed, the underlying pathology that leads to infertility expresses itself in variable degrees to different people and the severity of the outcomes is proportionately related to the severity of the infertility problem.

She added: "IVF and ICSI patients represent a group resistant to low-technology infertility treatment and have a longer infertility period; they may, accordingly, be selected by unknown factors associated with an increased risk of stillbirth." She is very right here! You see, she is getting closer but unfortunately, she will never get there unless she thinks of the “placental problem”.

Dr Wisborg and her colleagues are continuing to collect data in order to find answers to some of the questions on the association between stillbirths and fertility treatment. "One of the very important things to study in detail is the cause of stillbirth. We know from our data that gestational age at delivery was four weeks lower in stillborn infants of IVF pregnant women compared to stillborn infants of women who conceived spontaneously. However, despite the size of our study we did not have enough data to study this question in more detail," she said. You see! Here, despite the fact that the IVF stillbirth babies were born 4 weeks earlier than the stillbirth babies of fertile couples, she stated that the difference was not significant because we did not have enough numbers. In contrast, when she compared the rate of stillbirth between sub-fertile and fertile groups she stated that it was not different as if this were a fact. This is

scientifically unacceptable and shows the deliberate use of double standards within the same study. This really makes me very skeptical of Dr. Wisborg's overall results.
She concluded: "Hopefully, the results from our study emphasize the need for continuous follow-up of the outcome of fertility treatments, so that the information given to infertile couples seeking treatment can be differentiated to their individual circumstances." This is true but will yield no results of any significance unless the monitoring includes placental development during pregnancy and placental pathology after delivery. The placenta is the "log book" where nature records all the events that are important during pregnancy and define the quality of the pregnancy and its outcome as far as the death of the adult to be.

Between 1989 and 2006 there were several changes and improvements made in IVF techniques. However, the researchers say this is unlikely to have influenced their results as analyzing data stratified according to an early and a late study period made no changes to their conclusions. In addition, to preterm births, another potential confounding factor could be the so-called "vanishing twin" phenomenon. Around 10% of singleton pregnancies are thought to originate from twin gestations because of the transfer of two or more embryos. Compared with singleton conceptions, these pregnancies carry an increased risk of preterm delivery and low birth weight. However, the authors believe this is unlikely to be the sole reason for their results because the risk of stillbirth in non-IVF pregnancies was similar to that in fertile women. This last statement does not make any sense really! This is so out of line with real causes of increased rate of prematurity (3-fold increase), growth retardation (3-fold increase) and stillbirth (4-fold increase). Did Dr. Wisborg ever try to connect the dots? From her report it appears that she missed the forest for the trees. It has been so well established over the years that stillbirth babies as well as premature babies are growth retarded also. This is the result of a deficient placenta, which has been documented in thousands of pathology related studies. Similarly, hundreds of studies have shown without a doubt that small placental size, placental thrombosis and fetal vascular thrombosis are associated with adverse perinatal outcomes in as many as 75% of the pregnancies with such findings. Why is it then that no one ever looks at the placenta prenatally with the intent to prevent such outcomes by treating the placenta? The only explanation I have for this calamity is "inertia to change". As John Maxwell put it "The difficulty is not so much in developing new ideas as in escaping the old ones". The comfort of the common and familiar prevents us from changing because we feel uncomfortable or awkward to the detriment of our patients.

Reference:

(Wisborg K, Ingerslev HJ, Henriksen TB. Hum Reprod. 2010 May;25(5):1312-6. Epub 2010 Feb 23).