Consent for use of metformin in the preconceptual, and post-conception period.

Metformin**,** also known as glucophage**,** is a medication used alone or in combination with other medications to treat adults whose diabetes does not require insulin. It is thought to act by improving insulin binding thereby making the insulin that is available more effective and reducing the level of insulin that is needed in circulation.

In the last ten years, the field of reproductive medicine has identified a relationship between polycystic ovarian syndrome (PCOS) and detectable elevations in the amount of circulating insulin and plasminogen activating inhibitor-1 (PAI-1). PAI-1 inhibits the digestion of fibrin causing an increase in blood clot formation and fibrin deposition. **The use of metformin (as well as an amino acid called N-acetyl cysteine) in women with PCOS has corrected elevated PAI-1 levels and reversed the abnormal hormone levels associated with this condition.**

The use of metformin prior to conception in women who do not ovulate on a regular basis, such as is associated with PCOS, has been shown to produce regular ovulation, menstrual cycles, and pregnancy. This may be due, in part, to improved insulin receptor binding of IGF-1 (insulin-like growth factor-1) in the ovarian follicle that allows follicle stimulating hormone (FSH) from the brain to stimulate the follicle to grow. Without treatment, a woman with PCOS is 3-5 times more likely to suffer miscarriage and 2 times more likely to develop preeclampsia or pre-term labor. The cause of these complications are as yet unexplained, however, excessive fibrin deposition has been observed on the surface of the placenta in all disorders of reproduction, including miscarriage, pre-term labor, pregnancy-induced hypertension, intrauterine growth retardation, placental abruption, and stillbirth. This deposition of fibrin may block blood flow and cause a compromise in the maternal-fetal exchanges that occur across the placenta. Fibrin is a natural end-product in the clotting cascade that is normally kept in check through a balance between the clotting cascade and the fibrinolytic (fibrin digesting) pathways. Elevations in PAI-1, as is commonly seen in PCOS, inhibit fibrinolytic pathways and may be a cause of the fibrin deposition seen in the complications listed above. For these reasons, metformin is currently becoming a mainstay in the treatment of PCOS and oligoovulation (infrequent ovulation).

At the moment, the most pressing issue is whether to continue to use metformin once a pregnancy has been established. **The package insert for metformin categorizes it as class B drug suggesting that the merits of the medication should outweigh the risks when used in pregnancy. This does not suggest that metformin is teratogenic or harmful to a developing fetus, however, it indicates that there is essentially no data to support the safety of its use during pregnancy.**

During the past 10 years, experience has shown that PCOS patients who have been diagnosed with severe fibrinolytic imbalance benefit from the use of blood thinners such as heparin. While heparin is safe to use in pregnancy, its action is to reduce the clot formation, not to remove or digest fibrin once it is formed. As a result, heparin is a poor choice when treating the fibrinolytic disorder associated with PCOS. In addition, enormous amounts of heparin have been needed to keep clotting levels (aPTT) within a normal range. Heparin is also associated with bone loss and low platelet levels.

We recommend the use of metformin prior to conceiving and possibly also during your pregnancy. Our recommendations are based on each individual situation with consideration being given to such factors as fibrinolytic risk, history of pregnancy loss, and past perinatal morbidity. Those women most likely to be advised to continue metformin throughout the pregnancy are those who have demonstrated a significant fibrinolytic disorder with elevated PAI-1, elevated soluble fibrin monomer, history of infertility, oligoovulation, miscarriage, pre-term labor, preeclampsia, intra-uterine growth retardation, placental abruption, or stillbirth. Ultimately, the decision is yours. You should be aware that your obstetrician may not be comfortable with you taking metformin during pregnancy and you may have to stop. There is no data to determine what may happen when the metformin is stopped, perhaps, nothing.

Risks associated with taking metformin during pregnancy:

- The decision to take metformin during pregnancy is not a capricious one.
- The package insert states that metformin should not be taken during pregnancy.
- There is virtually no data about the use of metformin in pregnancy.
  The information that is available comes from South African and Dutch studies on non-insulin dependent pregnant women who took metformin to control their glucose levels (blood sugars) in pregnancy.
  - In 3 published studies, there were no reported fetal anomalies.
  - In one study, women taking metformin showed a higher incidence of preeclampsia than women taking insulin or sulfonureas.
  - In one pilot study, PCOS women who had experienced miscarriage in a previous pregnancy showed a significantly reduced rate of early miscarriage when they took metformin during the first trimester of pregnancy.
- Metformin can partially cross the placenta and therefore carries a theoretical risk to the newborn to have low blood sugars after delivery. This potential problem can be avoided with appropriate planning: either stop metformin one week prior to your expected date of delivery, or, inform your pediatrician to monitor your baby's blood sugar after delivery, so that intravenous glucose can be given if it is needed.

Simple risks associated with the use of metformin:

- Diarrhea: usually occurs shortly after eating, especially if the meal contains a lot of carbohydrates.
- Headaches: tend to occur initially, but resolve within a few days.

- Lactic acid build-up or metabolic acidosis: This is serious and potentially fatal condition. Symptoms include painful, burning muscles, stomach pain, severe headache, confusion, and rapid breathing.
- Death can occur from renal insufficiency or metabolic acidosis due to lactic acid build-up if metformin is not discontinued immediately. This is a very rare occurrence.

Alternatives:
- No metformin prior to conception or after a positive pregnancy test.
- Heparin, aspirin, and/or, superovulation.

I/We have read this consent and understand the information as it applies to me/us.

I/We have had the opportunity to ask questions and obtain answers in simple language.

I am/We are aware of the risks of not taking metformin (conception may be more difficult and the risk of early miscarriage higher).

I am/We are aware of the known and theoretical risks associated with taking metformin.

I understand that there are no guarantees or warrantees implied or made by my doctor's recommendations.

I/We (do/do not) consent to taking metformin prior to conception.

I/We (do/do not) consent to taking metformin while pregnant.

I/We understand that I may be considered a high-risk pregnancy and may require close observation during pregnancy.

_____ _____

Patient's signature Partner's signature

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Witness's signature