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LETTER TO THE EDITOR

Metformin and human uterine contractility

Mark P. Hehir · John J. Morrison

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Introduction

Metformin is primarily used clinically in the treatment of type 2 diabetes mellitus but in recent years has been suggested as a treatment for gestational diabetes mellitus (GDM) [1]. It has also been increasingly prescribed in the treatment of polycystic ovarian syndrome, and for recurrent early pregnancy loss in women with PCOS. Although Metformin has been used with increasing frequency in GDM, due to a lack of complete clinical data, its use has not gained universal acceptance. Tight glycemic control during pregnancy has, however been shown to bring both fetal and maternal benefits in cases of type 1 and type 2 diabetes [2].

Metformin is the most frequently prescribed oral hypoglycemic in the United States. It improves insulin sensitivity by activating AMP kinase, and is not associated with weight gain or hypoglycemia. Metformin (alone or with supplemental insulin) has not been found to be associated with increased perinatal complications when compared with insulin treatment, and it has also found favor with patients when compared with injectable insulin [3]. There is a significant body of evidence which indicates that metformin use in pregnancy appears to be associated with few adverse events [4], but this issue requires further evaluation. What has not been addressed is whether metformin may modulate uterine contractility during pregnancy, an issue which is central to its use. The aim of this study was to evaluate the effect of metformin on human uterine contractility in vitro.

M. P. Hehir (✉) · J. J. Morrison
Department of Obstetrics and Gynaecology,
Clinical Science Institute, University College Hospital Galway,
Newcastle Road, Galway, Ireland
e-mail: markhehir23@gmail.com

Methods

Biopsies of human myometrium were obtained at elective cesarean section in the third trimester of pregnancy. The biopsies were excised from the upper portion of lower uterine segment. Ethical committee approval for tissue collection was obtained and recruitment was by written informed consent. Once collected, tissue biopsies were placed in Krebs–Henseleit physiological salt solution (PSS). Myometrial strips were mounted for isometric recording under 2 g of tension in organ baths. Tissue baths contained 10 ml/s of PSS maintained at 37 °C, pH 7.4, and were gassed continuously with a mixture of 95 % oxygen/5 % carbon dioxide. Myometrial strips were allowed to equilibrate for 1 h. After equilibration, contractions occurred spontaneously or alternatively, were stimulated with oxytocin (0.5 nmol/L). Metformin was added to the tissue bath in a cumulative manner at bath concentrations of 1, 10, 100 nmol/L; 1 and 10 μmol/L at 20-min intervals. Control experiments were performed simultaneously. In all strips the integral of contractile performance was measured by calculating the area under the curve for a 20-min period for each drug concentration as previously described [5]. The mean maximum alteration in contractility (MMAC) of metformin represents the net final effect resulting from exposure to metformin after subtraction of any alteration observed in the control experiments.

Results

A control recording of spontaneous myometrial contractions is shown in Fig. 1a, in which the myometrial tissue is exposed to physiological salt solution only. Figure 1b demonstrates a recording of spontaneous myometrial

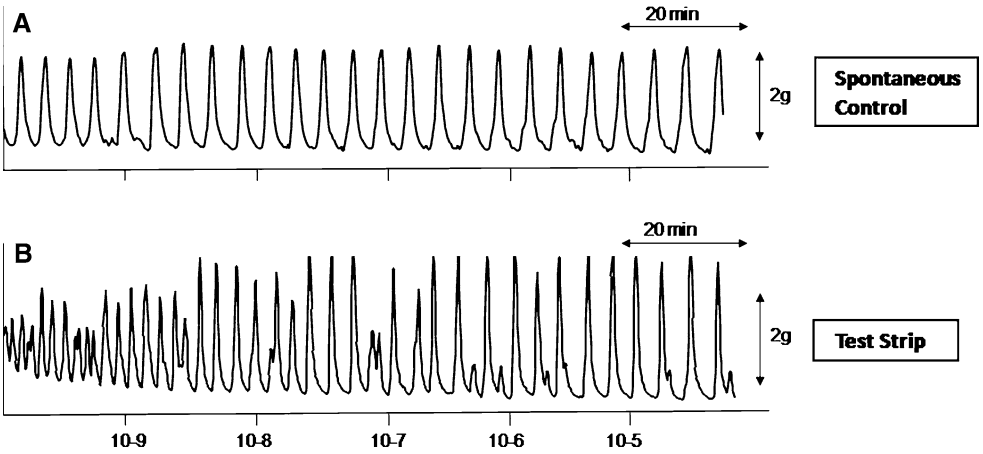

Fig. 1 Effects of metformin on spontaneous myometrial contractility in pregnant non-laboring tissue. Representative recordings demonstrating spontaneous contractions in a control strip (**a**), and the effects of cumulative additions of metformin (1 nmol/L–10 μmol/L) in 20 min intervals are shown (**b**)

contractions in tissue exposed to increasing concentrations of metformin (1 nmol/L–10 μmol/L). There was no alteration in the contractile pattern of strips exposed to metformin when compared to control strips exposed to just PSS. An MMAC of -1.77 ± 7.87 % was recorded ($n = 6$, $P > 0.05$). When oxytocin-induced myometrial contractions were exposed to metformin (1 nmol/L–10 μmol/L) similar effects were found. Metformin exerted an MMAC of $+1.5 \pm 8.09$ % ($n = 6$, $P > 0.05$) on oxytocin-induced contractions. There was no alteration in contractility for oxytocin-induced contractions, and the MMAC did not attain statistical significance when compared to control strips. In summary metformin had no effect on spontaneous or agonist-induced contractility in vitro.

Conclusion

The results from this study demonstrate that metformin does not exert any significant effect on the contractile pattern of spontaneous or oxytocin-induced myometrial contractions in an in vitro model. This lack of effect on contractility was observed across a wide range of concentrations (1 nmol/L–10 μmol/L). The findings were similar for spontaneous and oxytocin-induced myometrial contractions. The conclusions are therefore reliable and reproducible indicating no appreciable effect due to metformin exposure. There are, however other potential concerns for the use of metformin in pregnancy, not addressed in this study. Firstly, it is known that metformin crosses the placenta into the fetal circulation in late pregnancy, however, its effects on the feto-placental unit are largely unknown. Secondly, while there is no clear association between metformin use in pregnancy and increased incidence of congenital anomalies, some of the conditions that metformin is used to treat, such as infertility and gestational diabetes, are in themselves independent risk factors for congenital anomaly. It is clear that further data are required to evaluate the efficacy and safety of metformin use in pregnancy.

There are limitations to this study. The findings are all obtained from in vitro myometrial experiments, and hence may not truly reflect the in vivo situation. The samples of tissue used were all obtained from women undergoing cesarean section at term, and hence may not account for gestational alterations in myometrial function or sensitivity. The possibility that metformin may exert a genomic effect on human myometrium, with a delayed response, rather an immediate contractile effect, cannot be outruled. However, this series of experiments were well conducted in many different specimens, and there was consistently no observed alteration in myometrial contractile function, for both spontaneous and agonist-induced activity. This study therefore addresses one specific question in relation to metformin use in pregnancy, and the findings are reassuring. Future investigations should focus on the effects of metformin on the feto-placental vasculature.

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Conflict of interest The authors declare that they have no conflict of interest.

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